PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/165, 31/24, 31/44, 31/495, 31/535, C07C 229/38, 235/50, 237/08, C07D 213/64, 241/04, 265/30

A1

(11) International Publication Number: **WO 95/17888**

(43) International Publication Date: 6 July 1995 (06.07.95)

(21) International Application Number: PCT/US94/14684

(22) International Filing Date: 20 December 1994 (20.12.94)

(30) Priority Data:
08/176,357 30 December 1993 (30.12.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/176,357 (CIP)
Filed on 30 December 1993 (30.12.93)

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW 2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

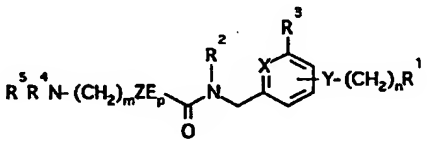
(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: DAINES, Robert, A. [US/US]; 2587 Cold Spring Road, Lansdale, PA 19446 (US).

(74) Agents: STEIN-FERNANDEZ, Nora et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

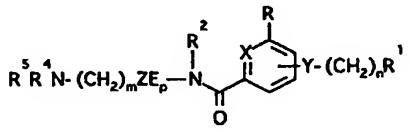
(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PT, RO, RU, SD, SI, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PHENYLMETHYL HEXANAMIDES, AND THE USE THEREOF



(I)



(II)

(57) Abstract

The present invention is to compounds of formula (I) or formula (II) or pharmaceutically acceptable salts thereof for the treatment of PKC-mediated disease states, wherein *inter alia* R^1 is hydrogen, lower alkyl or optionally substituted aryl; R^2 is hydrogen or lower alkyl; R^3 is hydrogen or $-(CH_2)_kR^6$, wherein R^6 is $-CO_2R^7$, $-NHC(O)R^7$, $-NR^7R^8$, or $-C(O)NR^7R^8$, wherein R^7 and R^8, independently from one another, are hydrogen, or alkyl provided that when R^6 is $-CO_2R^7$, R^7 is not hydrogen; R^4 and R^5, independently from one another, are hydrogen or lower alkyl, or wherein R^4 and R^5, together with the nitrogen to which they are bound, form a saturated or unsaturated 5-, 6-, or 7-membered ring; E is CH-R^9, wherein R^9 is hydrogen, alkoxy, -OH or $-NR^{10}R^{11}$, wherein R^{10} and R^{11}, independently from one another, are hydrogen or lower alkyl, or wherein R^{10} and R^{11}, together with the nitrogen to which they are bound, form a saturated or unsaturated 5-, 6-, or 7-membered ring; X is CH or N; Y is $-CH_2$ or -O, and further wherein Y is positioned on the central aromatic ring either ortho, meta or para relative to the amine containing side chain; Z is $-CH_2$ or optionally substituted aryl; k is an integer between 0 and 10; m is an integer between 0 and 10, provided that m is 0 only when Z is optionally substituted aryl or optionally substituted heteroaryl, and further, provided that when m is 0 and Z is optionally substituted aryl or optionally substituted heteroaryl, R^4 and R^5 are not hydrogen or lower alkyl; n is an integer between 6 and 20; and p is an integer between 0 and 1, provided that p must be 0 when Z is optionally substituted aryl or optionally substituted heteroaryl.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

PHENYLMETHYL HEXANAMIDES, AND THE USE THEREOF

FIELD OF THE INVENTION

This invention relates to phenylmethyl hexanamides and pharmaceutical compositions containing them. In addition, this invention relates to the use of phenylmethyl hexanamides as inhibitors of protein kinase C ("PKC"). Further, this invention relates to the treatment of PKC mediated disease states, including, but not limited to, chronic inflammatory and proliferative diseases such as psoriasis, neurological disorders and cancer, all in mammals, preferably humans, with the phenylmethyl hexanamides of this invention.

BACKGROUND OF THE INVENTION

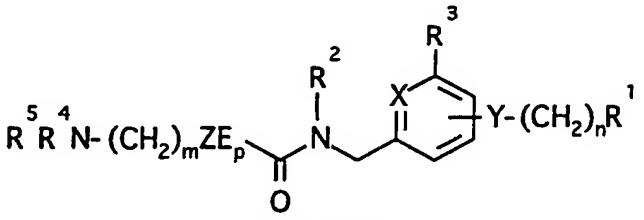
PKC, first discovered in 1977, is a member of a class of enzymes known as kinases that catalyze the transfer of a phosphate group from ATP to a substrate. PKC catalyzes phosphorylation of the amino acids serine and threonine. PKC is found in all tissue types and is believed to play a major role in cellular regulation, neurotransmission, tumor promotion, signal transduction, and cellular proliferation. Physiological activity of the enzyme is regulated by Ca^{2+}, diacylglycerol ("DAG"), and phosphotidylserine ("PS"). These modulators interact with the regulatory domain of the enzyme while substrate and ATP binding occur at the catalytic domain. Activators of the enzyme, such as phorbol esters, are known to cause intense inflammation and tumor promotion. Thus, compounds that are able to regulate the enzyme would be expected to be useful therapeutic agents for the treatment of chronic inflammatory and proliferative diseases, including, but not limited to, psoriasis, neurological disorders and cancer. An inhibitor of PKC would be expected to serve as such a regulating agent.

Most of the reported PKC inhibitors act via interaction with the catalytic domain of the enzyme. Few regulatory domain inhibitors have been reported. Since the catalytic domain of PKC has a high degree of homology with that of other kinases, it has been shown that many of the catalytic domain inhibitors exhibit activity against multiple kinases. Thus, the catalytic domain inhibitors are non-selective. However, since the regulatory domain of PKC has a structure unique to PKC, a compound that interacts with the regulatory domain of the enzyme would be expected to be a selective inhibitor. Thus, a regulatory domain inhibitor of PKC is highly desirable because it will have far less potential to inhibit non-target kinases.

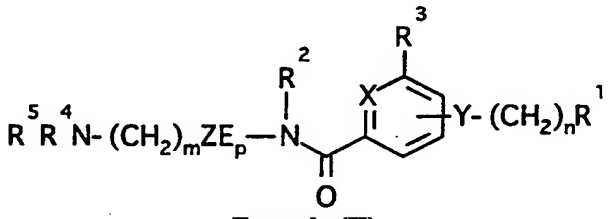
It has been found that the phenylmethyl hexanamides of this invention function as regulatory domain inhibitors of PKC and hence have utility in the prevention or therapeutic treatment of PKC mediated disease states.

SUMMARY OF THE INVENTION

In one aspect, the present invention is to compounds of formula (I) or formula (II) or pharmaceutically acceptable salts thereof:



Formula (I)



Formula (II)

wherein

R^1 is hydrogen, lower alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

R^2 is hydrogen or lower alkyl;

R^3 is hydrogen, $C{\equiv}CR^6$ or $-(CH_2)_kR^6$;

R^4 and R^5, independently from one another, are hydrogen or lower alkyl; or R^4 and R^5, together with the nitrogen to which they are bound, form a saturated or unsaturated 5-, 6-, or 7-membered ring;

R^6 is aryl, $-CO_2R^7$, $-NHC(O)R^7$, $-NR^7R^8$, or $-C(O)NR^7R^8$;

R^7 and R^8, independently from one another, are hydrogen, or alkyl, provided that when R^6 is $-CO_2R^7$, R^7 is not hydrogen;

E is CH-R^9, wherein R^9 is hydrogen, alkoxy, -OH or $-NR^{10}R^{11}$;

R^{10} and R^{11}, independently from one another, are hydrogen or lower alkyl, or wherein R^{10} and R^{11}, together with the nitrogen to which they are bound, form a saturated or unsaturated 5-, 6-, or 7-membered ring;

X is CH or N;

Y is $-CH_2$, -O, -S, -N or $C(O)NR^{12}R^{13}$, wherein R^{12} and R^{13} are, independently from one another, hydrogen or alkyl, and further wherein Y is positioned

on the central aromatic ring either ortho, meta or para relative to the amide containing side chain;

Z is $-CH_2$, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

k is an integer between 0 and 10;

m is an integer between 0 and 10, provided that m is 0 only when Z is optionally substituted aryl or optionally substituted heteroaryl, and further, provided that when m is 0 and Z is optionally substituted aryl or optionally substituted heteroaryl, R^4 and R^5 are not hydrogen or lower alkyl;

n is an integer between 6 and 20; and

p is an integer between 0 and 1.

In another aspect, the present invention is to pharmaceutical compositions comprising a compound of formula (I) or formula (II), and a pharmaceutically acceptable carrier therefor.

In yet another aspect, the present invention is to a method of treating PKC mediated disease states, including, but not limited to, chronic inflammatory and proliferative diseases such as psoriasis, neurological disorders and cancer, all in mammals, preferably humans, comprising administering to such mammal in need thereof, an effective amount of a compound of formula (I) or formula (II), or pharmaceutically active salts thereof.

In still another aspect, the present invention is in a method of inhibiting PKC in a mammal in need thereof, comprising administering to said mammal an effective amount of a compound of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that compounds of formula (I) and formula (II) are PKC inhibitors. It has also now been discovered that selective inhibition of PKC mediated mechanisms by treatment with a compound of formula (I) or formula (II), or a pharmaceutically acceptable salt thereof, represents a novel therapeutic and preventative approach to the treatment of a variety of disease states, including, but not limited to, chronic inflammatory and proliferative diseases such as psoriasis, neurological disorders and cancer, all in mammals, preferably humans.

The term "lower alkyl" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

The term "alkyl" is used herein at all occurrences to mean a straight or branched chain radical of 7 to 20 carbon atoms, unless the chain length is limited thereto, including, but not limited to heptyl, octyl, nonyl, decyl, dodecyl, and the like.

The term "alkoxy" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, bonded to an oxygen atom, including, but not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, and the like.

The terms "aryl" or "heteroaryl" are used herein at all occurrences to mean 5-14-membered optionally substituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems and, wherein one or more of the rings or ring systems may include one or more heteroatoms, which heteroatoms are selected from oxygen, nitrogen or sulfur. Representative examples include, but are not limited to, phenyl, naphthyl, pyridyl, quinolinyl, thiazinyl, furanyl, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, benzimidazole, and the like.

The term "halogen" is used herein at all occurrences to mean chloro, fluoro, iodo and bromo.

The term "5-, 6-, or 7-membered ring" is used at all occurrences to mean that substituents R^4 and R^5 and substituents R^7 and R^8, together with the nitrogen to which they are bound, form a saturated or unsaturated cyclic ring structure optionally containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur, including, but not limited to, morpholine, piperizine, piperidine, pyrrolidine, pyridine, and the like.

The terms "arylalkyl" and "heteroarylalkyl" are used herein at all occurrences to mean an aryl or heteroaryl moiety, respectively as defined above, that is connected to a C_{1-6} alkyl moiety as defined above, such as a benzyl group.

The term "optionally substituted" is used herein at all occurrences to mean that the moieties may or may not be substituted with, from one to three functional groups, including, but not limited to, alkyl, alkoxy, halogen, trifluoromethyl, nitro, cyano, amino, amido, hydroxy, aryl, heteroaryl, arylalkyl, and heteroarylalkyl.

The terms "optionally substituted aryl" or "optionally substituted arylalkyl" are used herein at all occurrences to mean an aryl ring (or the aryl ring of an arylalkyl moiety as defined above) which is optionally substituted with alkyl, alkoxy, halogen, trifluoromethyl, nitro, cyano, amino, amido, hydroxy, aryl, heteroaryl, arylalkyl, and heteroarylalkyl, preferably alkoxy, halo or trifluoromethyl, more preferably methoxy, ethoxy, chloro, fluoro or trifluoromethyl.

The term "optionally substituted heteroaryl" or "optionally substituted heteroarylalkyl" is used herein at all occurrences to mean a heteroaryl ring (or the

heteroaryl ring of a heteroarylalkyl moiety as defined above) which is optionally substituted with alkyl, alkoxy, halogen, trifluoromethyl, nitro, cyano, amino, amido, or hydroxy.

The term "central aromatic ring" is used herein at all occurrences to mean the aromatic ring of formula (I) or formula (II) which contains variable X.

As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not limited to, salts with organic acids such as hydrochloric, sulfate, phosphate, diphosphate, hydrobromide, and nitrate or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methansulfonate, p-toluensulfonate or palmitate, salicylate and stearate.

For the compounds of formulae (I) and (II) various embodiments are as follows.

R^1 is suitably hydrogen, lower alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl. R^1 is preferably hydrogen, lower alkyl or unsubstituted aryl, more preferably, hydrogen, methyl, ethyl or phenyl, most preferably hydrogen, methyl or ethyl.

R^2 is suitably hydrogen or lower alkyl. Preferably, R^2 is hydrogen, methyl or ethyl. More preferably, R^2 is hydrogen or methyl.

R^3 is suitably hydrogen, $C{\equiv}CR^6$ or $-(CH_2)_kR^6$. Preferably, R^3 is hydrogen or $-(CH_2)_kR^6$. When R^3 is $-(CH_2)_kR^6$, k is preferably an integer from 0 to 5, more preferably, an integer from 0 to 3 and R^6 is preferably $-NR^7R^8$ or $-CO_2R^7$. When R^6 is NR^7R^8, R^7 and R^8 are preferably hydrogen, or lower alkyl, more preferably hydrogen, methyl or ethyl, most preferably hydrogen. When R^6 is CO_2R^7, R^7 is preferably lower alkyl, most preferably methyl. When R^3 is $C{\equiv}CR^6$, R^6 is aryl, preferably phenyl.

R^4 and R^5, independently from one another, are suitably, hydrogen or lower alkyl; or R^4 and R^5, together with the nitrogen to which they are bound, form a saturated or unsaturated 5-, 6-, or 7-membered ring. Preferably, R^4 and R^5, independently from one another are hydrogen, methyl or ethyl. When R^4 and R^5, together with the nitrogen to which they are bound, form a six-membered ring, the ring is preferably a piperazine ring or a morpholine ring.

R^6 is suitably aryl, $-CO_2R^7$, $-NHC(O)R^7$, $-NR^7R^8$, or $-C(O)NR^7R^8$. Preferably, R^6 is $-NR^7R^8$ or $-CO_2R^7$.

R^7 and R^8, independently from one another, are suitably hydrogen, or alkyl, provided that when R^6 is $-CO_2R^7$, R^7 is not hydrogen. When R^6 is $-NR^7R^8$, R^7 and R^8, independently from one another are, preferably hydrogen or lower alkyl, more preferably, hydrogen or methyl, most preferably, R^7 and R^8 are each hydrogen. When

R^6 is $-CO_2R^7$, R^7 is preferably lower alkyl, more preferably C_1 to C_3 alkyl, most preferably methyl.

E is suitably CH-R^9, wherein R^9 is hydrogen, alkoxy, -OH or $-NR^{10}R^{11}$. It will be clear to the skilled artisan that for a compound of formula (II), R^9 can not be -OH or $-NR^{10}R^{11}$ because the compounds are potentially unstable.

R^{10} and R^{11}, independently from one another, are hydrogen or lower alkyl, or wherein R^{10} and R^{11}, together with the nitrogen to which they are bound, form a saturated or unsaturated 5-, 6-, or 7-membered ring. Preferably, E is CH-R^9, wherein R^9 is hydrogen or $-NR^{10}R^{11}$, more preferably, R^9 is hydrogen. When R^9 is $-NR^{10}R^{11}$, preferably, R^{10} and R^{11}, independently from one another, are hydrogen, methyl or ethyl, most preferably R^{10} and R^{11} are each hydrogen.

X is suitably CH or N. X is preferably CH.

Y is suitably $-CH_2$, -O, -S, -N or $-C(O)NR^{12}R^{13}$, wherein R^{12} and R^{13} are, independently from one another, hydrogen or alkyl, and further wherein Y is positioned on the central aromatic ring either ortho, meta or para relative to the amide containing side chain. Y is preferably $-CH_2$, -O or $-C(O)NR^{12}R^{13}$, more preferably $-CH_2$ or -O, most preferably -O. "Amide containing side chain", as used herein, refers to either the $C(O)-N(R^2)-CH_2-$ moiety of formula (I) or to the $-N(R^2)-C(O)-$ moiety of formula (II).

Z is suitably $-CH_2$, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl. Preferably, Z is CH_2 or optionally substituted aryl, more preferably, CH_2 or unsubstituted aryl, most preferably CH_2 or phenyl.

k is suitably an integer between 0 and 10; preferably k is an integer from 1 to 5.

m is an integer between 0 and 10, provided that m is 0 only when Z is optionally substituted aryl or optionally substituted heteroaryl, and further, provided that when m is 0 and Z is optionally substituted aryl or optionally substituted heteroaryl, R^4 and R^5 are not hydrogen or lower alkyl; preferably m is an integer from 1 to 8.

n is an integer between 6 and 20; preferably n is an integer from 8 to 12.

p is an integer between 0 and 1.

A preferred embodiment of this invention is to a compound of formula (I) or formula (II), wherein: X is CH or N, more preferably, X is CH; Z is $-CH_2$, or optionally substituted aryl; R^1 is hydrogen, lower alkyl or unsubstituted aryl, more preferably, R^1 is hydrogen or lower alkyl, most preferably, R^1 is hydrogen, methyl or ethyl; R^2 is hydrogen or unbranched lower alkyl, more preferably, R^2 is hydrogen, methyl or ethyl; R^3 is hydrogen or $-(CH_2)_kR^6$; R^4 and R^5, independently, from one another, are hydrogen, lower alkyl or R^4 and R^5, together with the nitrogen to which they are bound,

form a saturated or unsaturated 5-, 6- or 7-membered ring, more preferably, R^4 and R^5, independently, from one another, are hydrogen, lower alkyl or R^4 and R^5, together with the nitrogen to which they are bound, form a saturated six-membered ring, most preferably, R^4 and R^5, independently, from one another, are hydrogen or lower alkyl; R^6 is $-NR^7R^8$ or $-CO_2R^7$, wherein R^7 and R^8 are, independently from one another, hydrogen or alkyl, provided that when R^6 is $-CO_2R^7$, R^7 is not hydrogen; more preferably, R^6 is NH_2 or CO_2CH_3. [When R^3 is $-(CH_2)_kR^6$ and R^6 is $-NR^7R^8$, R^7 and R^8 are most preferably hydrogen. When R^3 is $-(CH_2)_kR^6$ and R^6 is $-CO_2R^7$, R^7 is preferably lower alkyl, more preferably methyl or ethyl, most preferably methyl.] E is CH-R^9, wherein R^9 is hydrogen or $-NR^{10}R^{11}$, wherein R^{10} and R^{11}, independently from one another, are hydrogen or lower alkyl, or wherein R^{10} and R^{11}, together with the nitrogen to which they are bound, form a saturated or unsaturated 5-, 6-, or 7-membered ring, more preferably, E is CH-R^9, wherein R^9 is hydrogen or $-NR^{10}R^{11}$, wherein R^{10} and R^{11}, independently from one another, are hydrogen, most preferably, E is CH-R^9, wherein R^9 is hydrogen; k is an integer between 0 and 10; more preferably, k is an integer between 0 and 5; m is an integer between 0 and 10, provided that m is 0 only when Z is optionally substituted aryl or optionally substituted heteroaryl, and further, provided that when m is 0 and Z is optionally substituted aryl or optionally substituted heteroaryl, R^4 and R^5 are not hydrogen or lower alkyl; more preferably, m is an integer from 1 to 8; n is an integer between 6 and 20; more preferably, n is an integer from 8 to 15; most preferably, n is an integer from 10 to 13; and p is an integer between 0 and 1.

Among the preferred compounds of the invention are the following:
(*R*)-2,6-diamino-N-[[2-dodecyloxy)phenyl]methyl]-N-methylhexanamide;
6-amino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylhexanamide;
6-amino-N-methyl-N-[[[2-(8-phenyl)octyloxy]phenyl]methyl]hexanamide;
(*R*)-2,6-diamino-N-methyl-N-[[[2-(8-phenyl)octyloxy]phenyl]methyl] hexanamide;
6-amino-N-[[2-(hexadecyloxy)phenyl]methyl]-N-methylhexanamide;
4-amino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylbutanamide;
6-amino-N-[[3-(dodecyloxy)phenyl]methyl]-N-methylhexanamide;
N-[[2-(dodecyloxy)phenyl]methyl]-N-methyl-6-morpholinohexanamide;
N-[[2-(dodecyloxy)phenyl]methyl]-N-[methylhexanamido]-6-N′, N′, N′-trimethylammonium bromide;
6-amino-N-methyl-N-[[[2-(8-phenyl)octyl]phenyl]methyl]hexanamide;
N-[[(5-amino-2-dodecyloxy)phenyl]methyl]-6-amino-N-methylhexanamide;
6-amino-N-[[2-dodecyloxy-5-[(1-oxooctyl)amino]phenyl]methyl]-N-methylhexanamide;
6-amino-N-[[2-(dodecyloxy)phenyl]methyl]hexanamide;

6-amino-N-[(3-dodecyloxy)-2-pyridinyl]methyl]-N-methylhexanamide;
N-(6-aminohexane-1-yl)-2-dodecyloxybenzamide;
N-(6-aminohexane-1-yl)-2-dodecyloxy-5-(2-methoxycarbonylethyl)benzamide;
N-[4-(2-amino)ethyl]phenyl-2-dodecyloxybenzamide;
N-(6-aminohexane-1-yl)-5-[(3-amino)propyl]-2-dodecyloxybenzamide ;
N-[3-(3-amino)propyl]phenyl-2-dodecyloxybenzamide;
N-[2-(3-amino)propyl]phenyl-2-dodecyloxybenzamide;
5-(2-phenylethynyl)-N-(6-aminohexan-1-yl)-2-dodecyloxybenzamide;
5-(2-phenylethyl)-N-(6-aminohexan-1-yl)-2-dodecyloxybenzamide;
6-amino-N-[[3-[(N-dodecyl)aminocarbonyl]phenyl]methyl]hexanamide;
N-(6-aminohexan-1-yl)-2-dodecyloxy-5-phenylbenzamide;
N-(2-piperazinyl)phenyl-2-dodecyloxybenzamide;
N-(3-piperazinyl-4-methoxy)phenyl-2-dodecyloxybenzamide; and
5-(3-aminopropyl)-2-dodecyloxy-N-(3-piperazinyl-4-methoxy)phenylbenzamide;

Methods of Preparation

The present compounds of formulae (I) and (II) can be prepared by art-recognized procedures from known or commercially available starting materials. Several different synthetic schemes can be used to prepare the compounds of this invention and are described in greater detail below.

As a general summary of the synthetic pathways described in greater detail below the compounds of formulae (I) and (II) can be produced by the following means. One of ordinary skill in the art given this disclosure of how to make specific compounds of the invention would understand how to make analogous compounds of formula (I) and formula (II) that are within the scope of the instant invention.

A) To prepare the intermediate compounds which are used in preparing a compound of formula (I), wherein Y is O (see Schemes 1, 2, 3, 5 and 6 shown below) an optionally substituted hydroxybenzaldehyde (such as ortho salicylaldehyde, meta salicylaldehyde or 5-nitro salicylaldehyde all commercially available from Aldrich®, Milwaukee, WI) is alkylated with an appropriate commercially available or conventionally prepared alkylating agent (such as 1-iodododecane, phenyloctylbromide, hexadecyliodide) under mild basic conditions (such as K_2CO_3, Cs_2CO_3) in an aprotic solvent (such as dimethylformamide ["DMF"], dimethyl sulfoxide ["DMSO"] or acetone) at elevated temperatures (such as 85°C to 90°C). The alkylating agent is chosen appropriately, depending upon the chain length desired for the substituent on the central aromatic ring.

B) Conversion of the aldehyde moiety on the intermediate prepared according to step (A) above to an N-alkyl amino moiety, is accomplished by dissolving the intermediate in an appropriate solvent (such as methanol, ethanol or methylene chloride) and treating the solution with methylamine hydrochloride, sodium cyanoborohydride and sodium acetate at room temperature, followed by work up with concentrated acid (such as HCl) and then basification with strong base (such as NaOH); and, if desired, subsequent purification.

C) Conversion of the amino intermediate prepared according to step (B) above to a protected amide of formula (I), is accomplished by adding to the amine, which is dissolved in an aprotic solvent (such as methylene chloride), a suitable base (such as 4-methylmorpholine or triethylamine); and a suitable activated ester or a suitable acid chloride or a suitable carboxylic acid which acid is in the presence of a peptide coupling reagent [such as Nα, Nε-di-tert-butoxycarbonyl-L-lysine N-hydroxysuccinimide ester or (tert-butoxycarbonyl)-ε-aminocaproic acid; suitable peptide coupling reagents for use with the carboxylic acid are 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride ("EDC") or dicyclohexylcarbodiimide ("DCC")], followed by addition of 1-hydroxy-benzotriazole hydrate ("HOBT"). After the reaction is complete, the mixture is quenched with a suitable base (such as N,N-dimethylethylenediamine), followed by a standard work up and, if desired, subsequent purification.

D) The amide intermediate prepared according to step (C) is deprotected using standard procedures such as treatment with an acid (such as trifluoroacetic acid ("TFA") or HCl) in an aprotic solvent (such as methylene chloride or dioxane). The acid salt may be isolated at this point or the free base obtained by neutralization (see Schemes 1, 2, 4-8, 9, and 10-12).

E) To prepare a compound of formula (I), wherein R^4 and R^5, together with the nitrogen to which they are bound form a 6-membered morpholino ring, the above steps (A) and (B) are performed. Conversion of the amino intermediate prepared according to step (B) to an amide such as is depicted by 12-Scheme 3, is accomplished by acylating the amino group with a suitable acid halide (such as 6-bromo-hexanoyl chloride or octanoyl chloride) in an aprotic solvent (such as methylene chloride) at room temperature or below.

F) Alkylation of the intermediate prepared according to step (E) is performed by adding a heterocyclic amine (such as morpholine, or a protected piperazine or a suitable tertiary amine such as trimethylamine) to a solution of the intermediate in an aprotic solvent (such as DMF or DMSO) in an inert atmosphere (such as argon). Standard work up and purification, if desired, follows.

G) To prepare compounds of formula (I), wherein Y is $-CH_2$, the procedures of PCT/US93/02803, published September 30, 1993 as WO 93/19035, specifically at page 15, Example 7, which is incorporated by reference herein, are used to make an aldehyde intermediate such as depicted below as 15-Scheme 4. The intermediate is converted to an amino intermediate, followed by amide formation and deprotection according to steps (B), (C) and (D) discussed above.

H) To prepare compounds of formula (I), wherein R^3 is NH_2, steps (A), (B) and (C) are performed on a nitro hydroxybenzaldehyde (such as 5-nitro salicylaldehyde). The protected nitro intermediate thus formed is reduced to the amino intermediate (see Scheme 5) using standard reduction conditions (such as palladium on carbon, in an H_2 atmosphere). The above amine-containing compound is deprotected according to step (D) discussed above.

I) To prepare compounds of formula (I), wherein R^3 is $-NHC(O)R^7$, and R^7 is alkyl, the amino compound prepared according to step (H) is prepared and then acylated according to step (E), with subsequent deprotection according to step (D).

J) An alternative method for preparing compounds of formula (I), wherein Y is O, is to start the synthesis with 2-hydroxybenzamide (Aldrich) which is alkylated according to step (A) above. The amide intermediate thus formed is then converted to an amine using conventional techniques such as reduction with $LiAlH_4$ in THF, followed by steps (C) and (D).

K) To prepare compounds of formula (I), wherein X is N, step (A) is performed on a hydroxypyridino compound such as 3-hydroxy-2-(hydroxymethyl)pyridine (Aldrich). The resulting alkylated hydroxymethyl intermediate is oxidized to an aldehyde with a suitable oxidizing agent (such as manganese dioxide or pyridinium chlorochromate) in an aprotic solvent (such as methylene chloride). Steps (B), (C) and (D) are performed on the oxidized intermediate (see Scheme 8).

L) To prepare a compound of formula (II), wherein Y is O, acetylsalicyloyl chloride (Aldrich) is converted to an amide by treating a solution of N-Boc-1, 6-diaminohexane hydrochloride (commercially available from Fluka, Ronkonkoma, NY) in pyridine with the acid chloride. After the reaction is complete, the mixture is diluted with an aprotic solvent (such as methylene chloride or ethyl acetate) and poured into dilute acid (such as 10% HCl), which gives an amidoarylacetoxy intermediate after standard work up. This intermediate is dissolved in a protic solvent (such as methanol or ethanol) and treated with an excess of base (such as potassium carbonate), after which the mixture is poured into aqueous ammonium chloride and the desired Boc-protected hydroxyamide is extracted with an aprotic solvent (such as methylene chloride or

ethyl acetate). The Boc-protected hydroxyamide is then alkylated according to step (A) above, and deprotected according to step (D) above.

M) To prepare a compound of formula (II), wherein R^3 is $-(CH_2)_kR^6$; R^6 is $-CO_2R^7$; and R^7 is alkyl, the carboxylic acid moiety of 5-formylsalicylic acid is converted to an amide by following the procedures of step (C) above, except N-(tert-butoxycarbonyl)-1,6 diaminohexane dihydrochloride is substituted for (2-dodecyloxy)-N-benzylamine and 5-formylsalicylic acid is substituted for (tert-butoxycarbonyl)-ε-aminocaproic acid. Using the amido intermediate thus formed, alkylation step (A) is performed as discussed above.

N) The aldehyde moiety of the intermediate prepared according to step (M) may be converted to a vinyl ester by dissolving it in an aprotic solvent (such as toluene) and treating it with methyl(triphenylphosphoranylidene)acetate and heated (to reflux, preferably, 50°C). The vinyl ester is reduced according to step (H) above and deprotected according to step (D) above.

O) To prepare a compound of formula (II), wherein Z is phenyl, 4-nitro-phenethylamine hydrochloride (Aldrich) is added to a cooled solution of di-tert-butyl dicarbonate (Aldrich) in an aprotic solvent (such as DMF), after which, when the reaction is complete, a standard work up and purification, if desired, are performed in order to form a protected amino intermediate.

P) The nitro moiety on the protected nitroamino compound prepared according to step (O) is reduced to an amino moiety according to step (H) above.

Q) The unprotected amino moiety on the diamine prepared according to step (P) is converted to an amide according to steps (B) and (C) using salicylic acid instead of (tert-butoxycarbonyl)-ε-aminocaproic acid. (See Scheme 11)

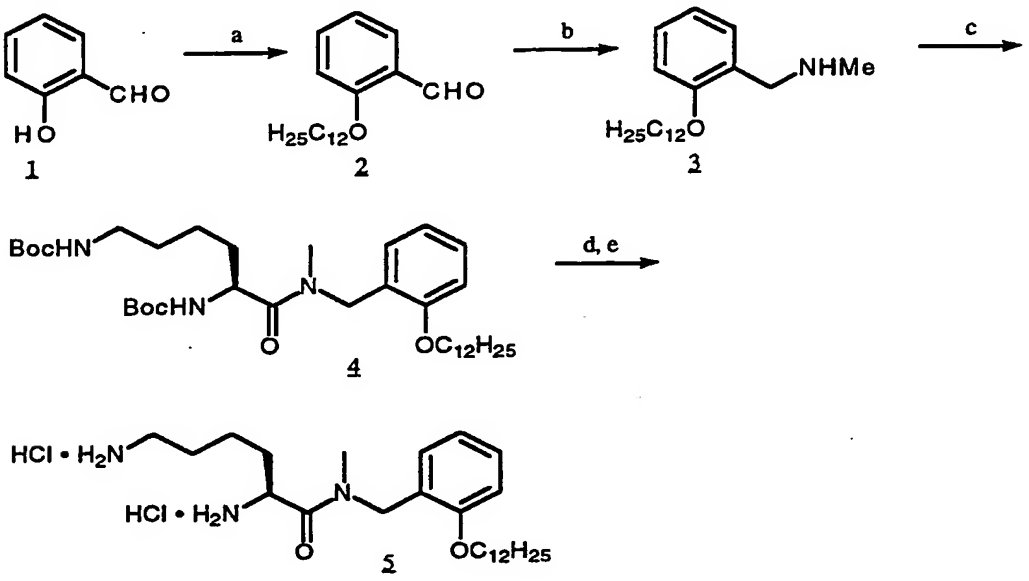
R) To prepare a compound of formula (II), wherein R^3 is $-(CH_2)_kR^6$, wherein R^6 is NR^7R^8, the method according to step (C) is performed by converting an acid (such as 5-iodosalicylic acid) into an amide by using N-Boc-1, 6-diaminohexane hydrochloride instead of (2-dodecyloxy)-N-benzylamine; which intermediate may be alkylated according to step (A) above.

S) Conversion of the iodo moiety into a protected amino moiety on the above alkylated intermediate prepared according to step (R), is accomplished by dissolving the alkylated intermediate in an amine base (such a triethylamine) under an inert atmosphere (such as argon) and adding bis(triphenylphosphine)palladium(II) chloride and copper(I) iodide, wherein said mixture is heated (to about 50°C), cooled, worked up by standard procedures and purified, if desired. The protected amino moiety is reduced according to step (H) and deprotected according to step (D) above. Alternatively, the

palladium coupling may be accomplished by coupling to a boronate (Scheme 15) instead of an acetylene (Scheme 12)

The following Schemes illustrate the reaction conditions and reagents used for preparing specific compounds of the invention.

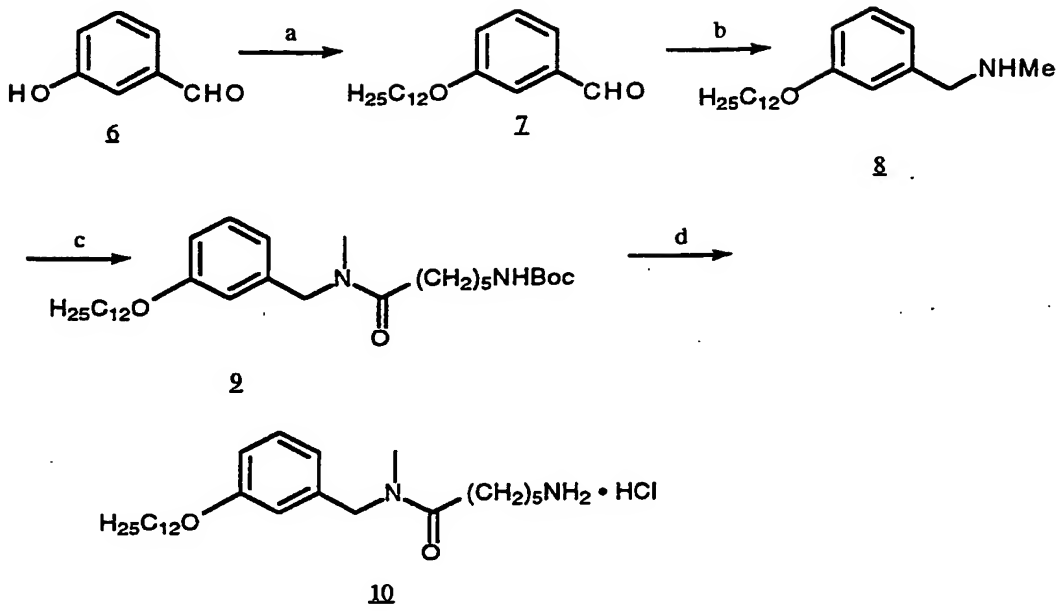
Scheme 1 (Examples 1, 2, 3, 4, 5, and 6)



a) $C_{12}H_{25}I$, K_2CO_3, DMF, 90 °C; b) $MeNH_2 \cdot HCl$, $NaCNBH_3$, NaOAc, MeOH; c) Nα,Nε-di-tert-butoxycarbonyl-L-lysine N-hydroxysuccinimide ester, HOBT, NMM, CH_2Cl_2; d) TFA, CH_2Cl_2; e) 0.1N HCl.

Scheme 1 illustrates the preparation of a specific compound of formula (I) wherein $-Y(CH_2)_nR^1$ is $-OC_{12}H_{25}$; R^2 is methyl; R^3 is hydrogen; X is CH; E is $-NH_2$; Z is $-CH_2$; m is 3; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention.

Scheme 2 (Example 7)

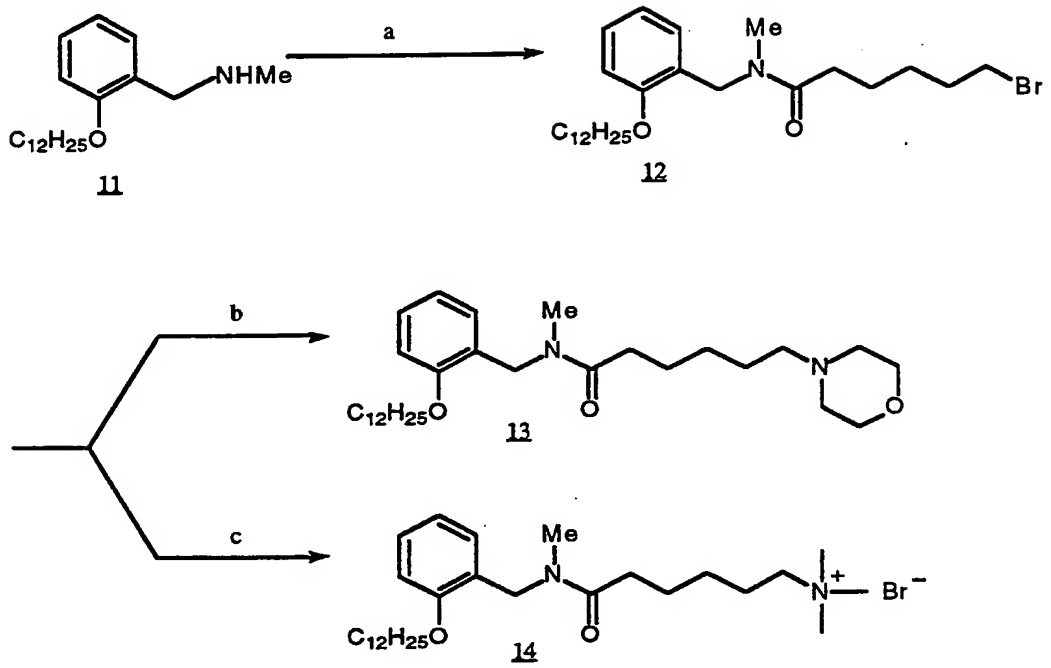


6 7 8 9 10

a) $C_{12}H_{25}I$, K_2CO_3, DMF, 90 °C; b) $MeNH_2 \cdot HCl$, $NaCNBH_3$, NaOAc, MeOH; c) (tert-butoxycarbonyl)-ε-aminocaproic acid, EDC, HOBT, NMM, CH_2Cl_2; d) 4N HCl/dioxane.

Scheme 2 illustrates the preparation of a specific compound of formula (I) wherein $-Y(CH_2)_nR^1$ is $-OC_{12}H_{25}$; R^2 is methyl; R^3 is hydrogen; X is CH; E is $-CH-R^9$, wherein R^9 is hydrogen; Z is $-CH_2$; m is 3; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention.

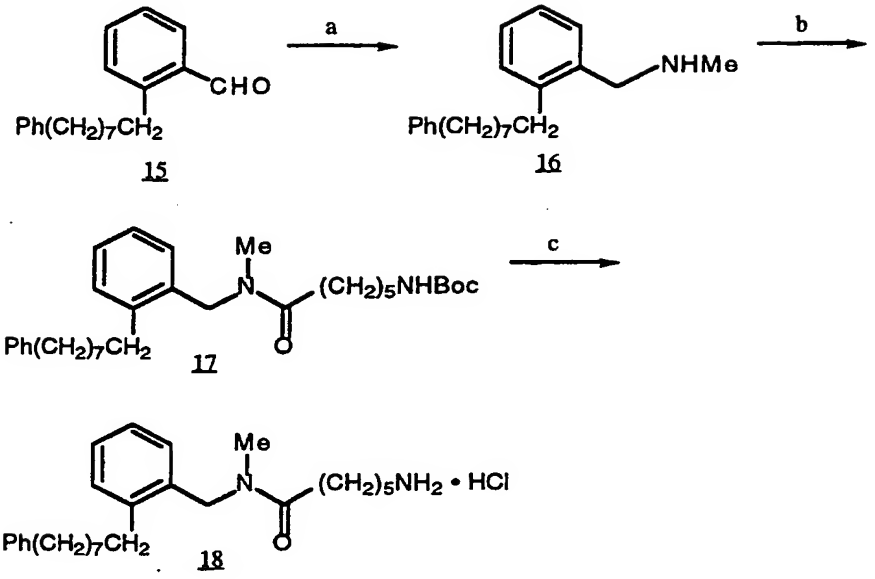
Schem 3 (Exampl s 8 and 9)



a) 6-bromo-hexanoyl chloride, CH_2Cl_2, 0 °C; b) morpholine, DMF; c) Me_3N, DMF.

Scheme 3 illustrates the preparation of a specific compound of formula (I) wherein $-Y(CH_2)_nR^1$ is $-OC_{12}H_{25}$; R^2 is methyl; R^3 is hydrogen; X is CH; E is $-CH-R^9$, wherein R^9 is hydrogen; Z is $-CH_2$; m is 3; and R^4 and R^5 independently from one another are hydrogen or, wherein R^4 and R^5, together with the nitrogen to which they are bound, form a 6-membered ring. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention.

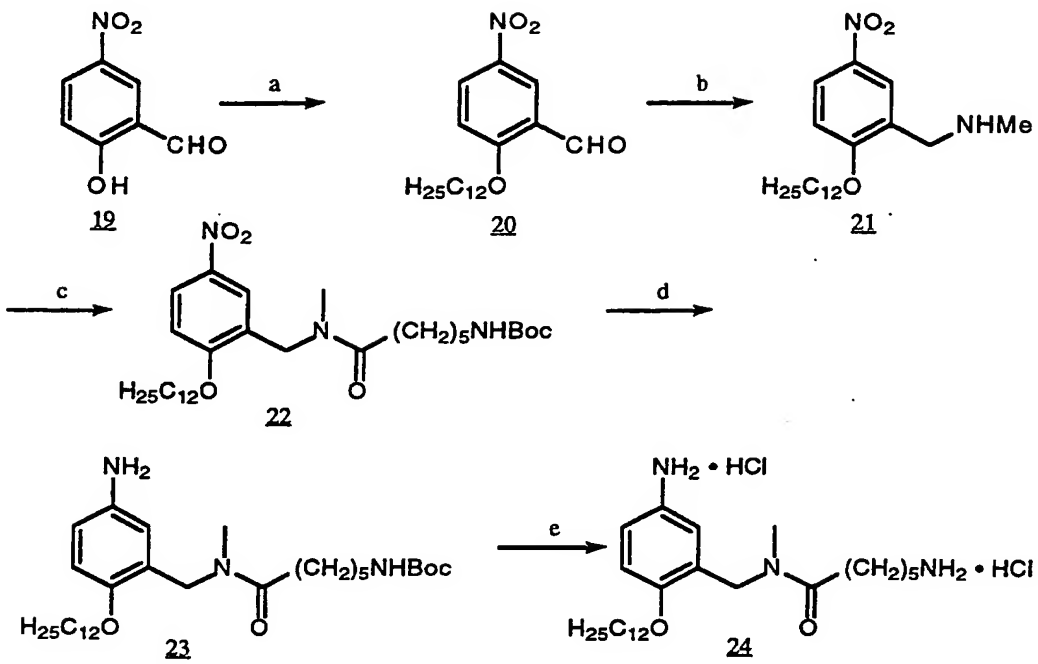
Scheme 4 (Example 10)



a) $MeNH_2$ • HCl, $NaCNBH_3$, NaOAc, MeOH; b) (tert-butoxycarbonyl)-ε-aminocaproic acid, EDC, HOBT, NMM, CH_2Cl_2; c) 4N HCl/dioxane.

Scheme 4 illustrates the preparation of a specific compound of formula (I) wherein $-Y(CH_2)_nR^1$ is $-CH_2(CH_2)_7Ph$; R^2 is methyl; R^3 is hydrogen; X is CH; E is $-CH-R^9$, wherein R^9 is hydrogen; Z is $-CH_2$; m is 3; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention.

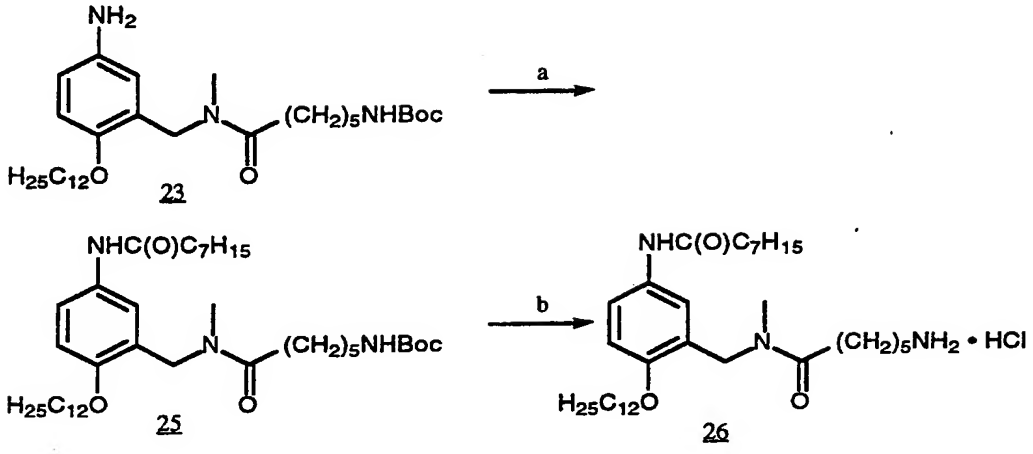
Scheme 5 (Example 11)



a) $C_{12}H_{25}I$, K_2CO_3, DMF, 90 °C; b) $MeNH_2$ • HCl, $NaCNBH_3$, NaOAc, MeOH; c) (tert-butoxycarbonyl)-ε-aminocaproic acid, EDC, HOBT, NMM, CH_2Cl_2; d) 10% Pd/C, H_2, MeOH-EtOAc; e) 4N HCl/dioxane.

Scheme 5 illustrates the preparation of a specific compound of formula (I) wherein $-Y(CH_2)_nR^1$ is $-OC_{12}H_{25}$; R^2 is methyl; R^3 is $-NR^7R^8$, wherein R^7 and R^8 are each hydrogen; X is CH; E is $-CH-R^9$, wherein R^9 is hydrogen; Z is $-CH_2$; m is 3; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention.

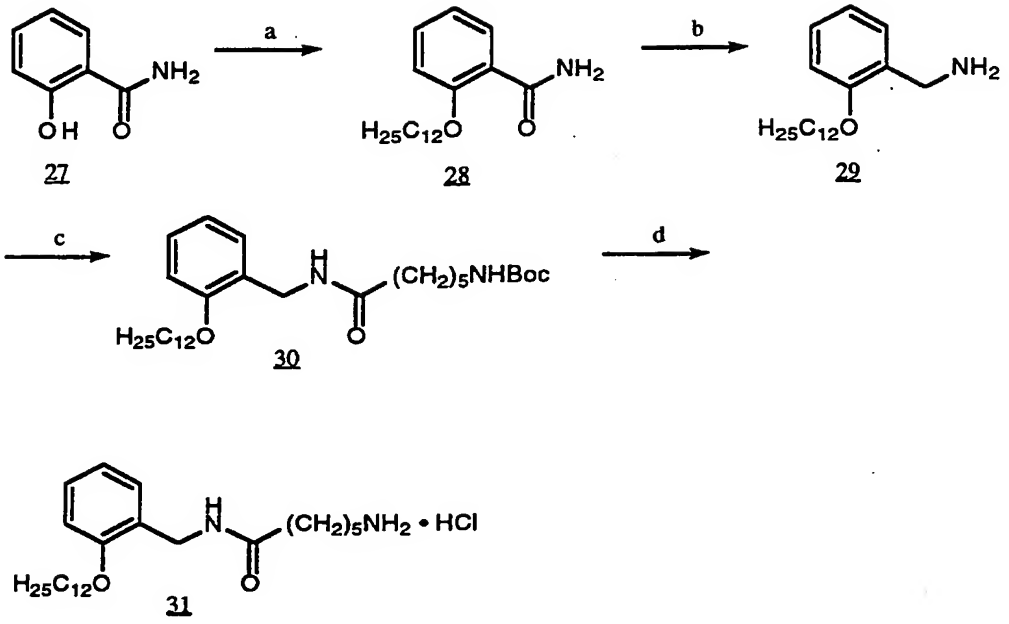
Scheme 6 (Example 12)



a) $C_7H_{15}COCl$, CH_2Cl_2, 0 °C; b) 4N HCl/dioxane.

Scheme 6 illustrates the preparation of a specific compound of formula (I) wherein $-Y(CH_2)_nR^1$ is $-OC_{12}H_{25}$; R^2 is methyl; R^3 is $-NHC(O)R^7$, wherein R^7 is alkyl; X is CH; E is $-CH-R^9$, wherein R^9 is hydrogen; Z is $-CH_2$; m is 3; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention.

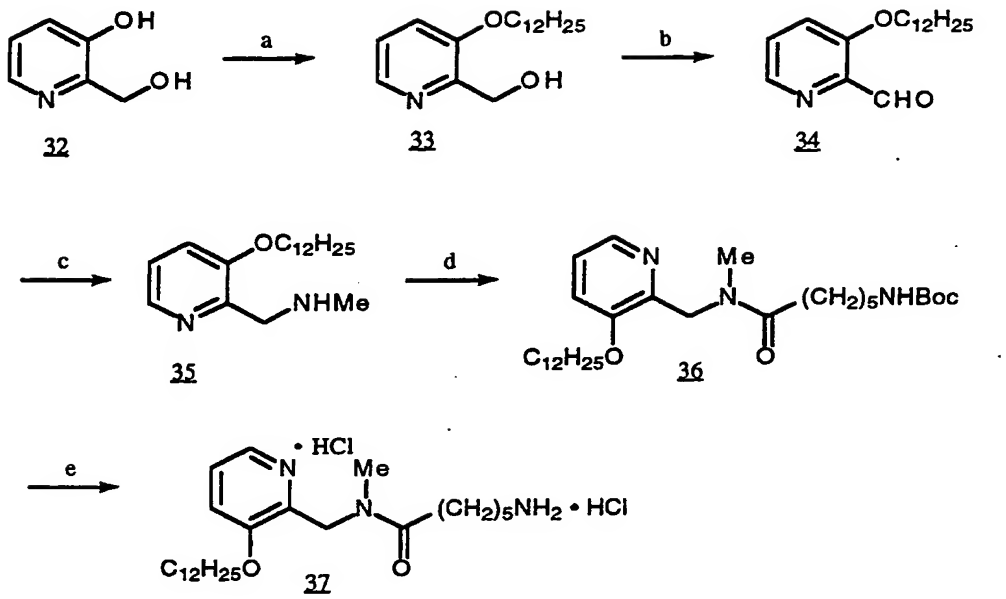
Scheme 7 (Example 13)



a) $C_{12}H_{25}I$, K_2CO_3, DMF, 90 °C; b) 0.1M $LiAlH_4$/THF, THF; c) (tert-butoxycarbonyl)-ε-aminocaproic acid, EDC, HOBT, NMM, CH_2Cl_2; d) 4N HCl/dioxane.

Scheme 7 illustrates the preparation of a specific compound of formula (I) wherein $-Y(CH_2)_nR^1$ is $-OC_{12}H_{25}$; R^2 is hydrogen; R^3 is hydrogen, X is CH; E is $-CH-R^9$, wherein R^9 is hydrogen; Z is $-CH_2$; m is 3; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention.

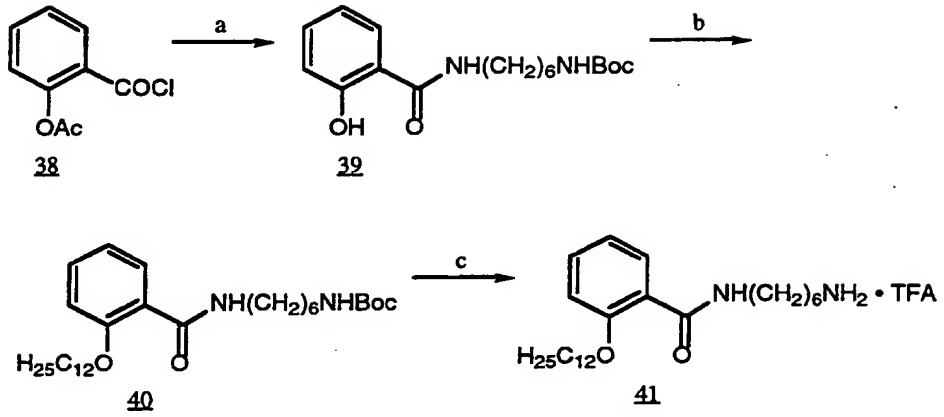
Scheme 8 (Example 14)



a) $C_{12}H_{25}I$, K_2CO_3, DMF, 90 °C; b) MnO_2, CH_2Cl_2; c) $MeNH_2$ • HCl, $NaCNBH_3$, NaOAc, MeOH; d) (tert-butoxycarbonyl)-ε-aminocaproic acid, EDC, HOBT, NMM, CH_2Cl_2; e) 4N HCl/dioxane.

Scheme 8 illustrates the preparation of a specific compound of formula (I) wherein $-Y(CH_2)_nR^1$ is $-OC_{12}H_{25}$ R^2 is methyl; R^3 is hydrogen; X is N; E is $-CH-R^9$, wherein R^9 is hydrogen; Z is $-CH_2$; m is 3; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention.

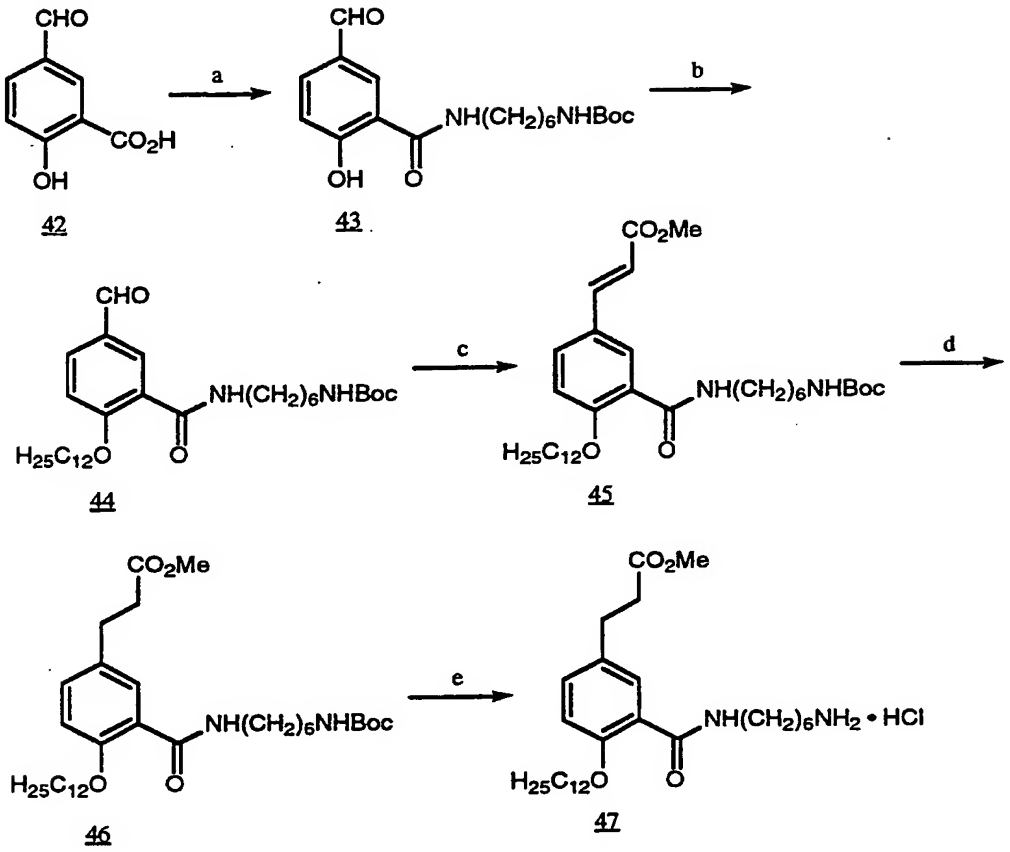
Scheme 9 (Example 15)



a) HCl • $H_2N(CH_2)_6NHBoc$, pyridine, then K_2CO_3, MeOH; b) $C_{12}H_{25}I$, Cs_2CO_3, DMF, 85 °C; c) TFA, CH_2Cl_2.

Scheme 9 illustrates the preparation of a specific compound of formula (II) wherein $-Y(CH_2)_nR^1$ is $-OC_{12}H_{25}$; R^2 is hydrogen; R^3 is hydrogen; X is CH; E is $-CH-R^9$, wherein R^9 is hydrogen; Z is $-CH_2$; m is 4; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention.

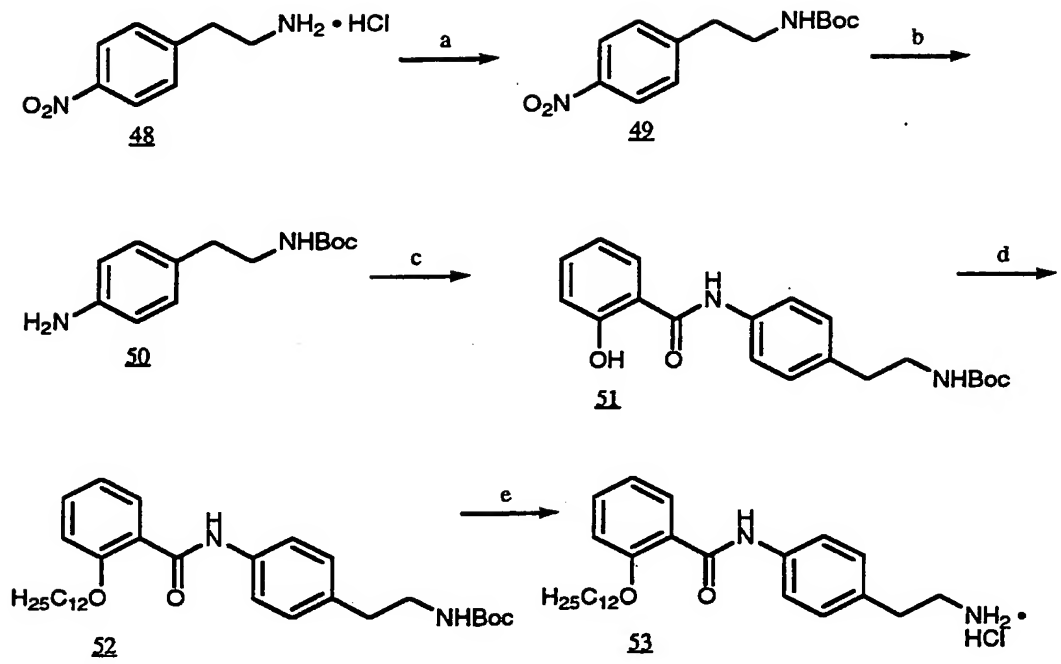
Scheme 10 (Example 16)



a) HCl • $H_2N(CH_2)_6NHBoc$, EDC, HOBT, NMM, CH_2Cl_2; b) $C_{12}H_{25}I$, Cs_2CO_3, DMF, 85 °C; c) $Ph_3P{=}CHCO_2Me$, toluene, 50 °C; d) 10% Pd/C, H_2, MeOH-EtOAc; e) 4N HCl, dioxane.

Scheme 10 illustrates the preparation of a specific compound of formula (II) wherein $-Y(CH_2)_nR^1$ is $-OC_{12}H_{25}$; R^2 is hydrogen; R^3 is $-(CH_2)_kR^6$, wherein k is 2 and R^6 is $-CO_2R^7$, wherein R^7 is methyl; X is CH; E is $-CH-R^9$, wherein R^9 is hydrogen; Z is $-CH_2$; m is 4; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention.

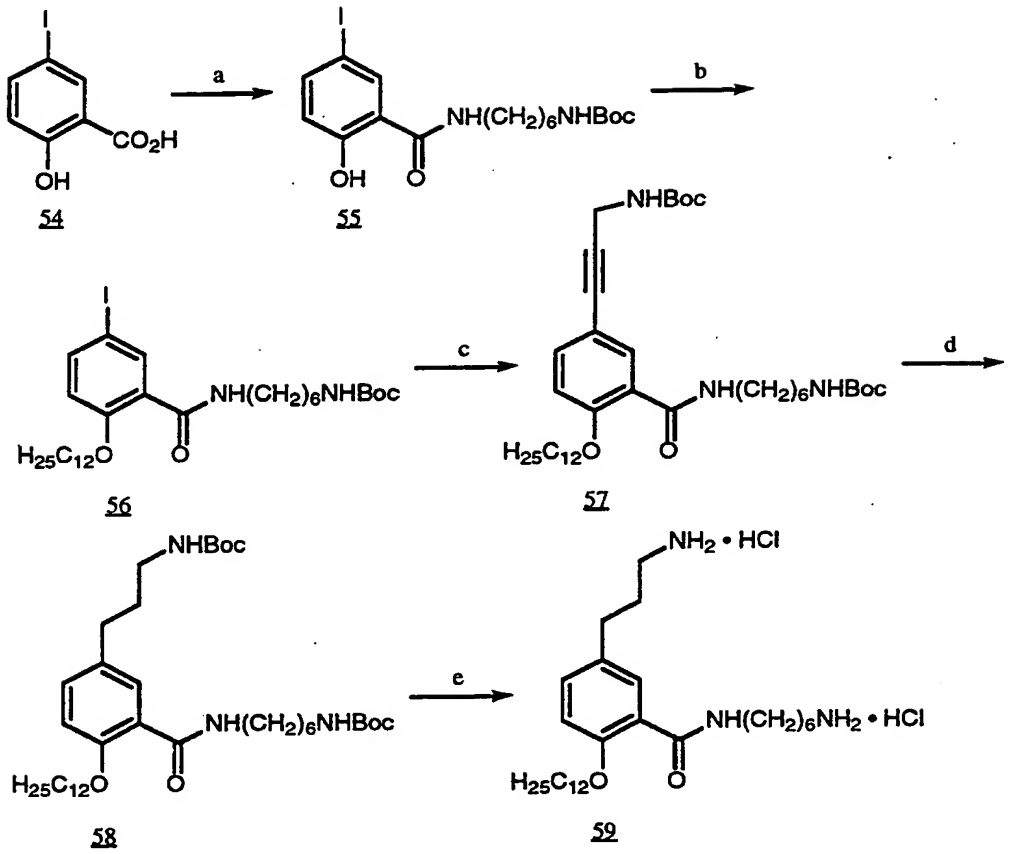
Scheme11 (Example 17)



a) Boc_2O, pyridine, DMF; b) 10% Pd/C, H_2, MeOH; c) salicylic acid, EDC, HOBT, NMM, CH_2Cl_2; d) $C_{12}H_{25}I$, Cs_2CO_3, DMF, 85 °C; e) 4N HCl, dioxane.

Scheme 11 illustrates the preparation of a specific compound of formula (II) wherein $-Y(CH_2)_nR^1$ is $-OC_{12}H_{25}$; R^2 is hydrogen; R^3 is hydrogen; X is CH; Z is $-CH_2$; m is 1; p is 0; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention.

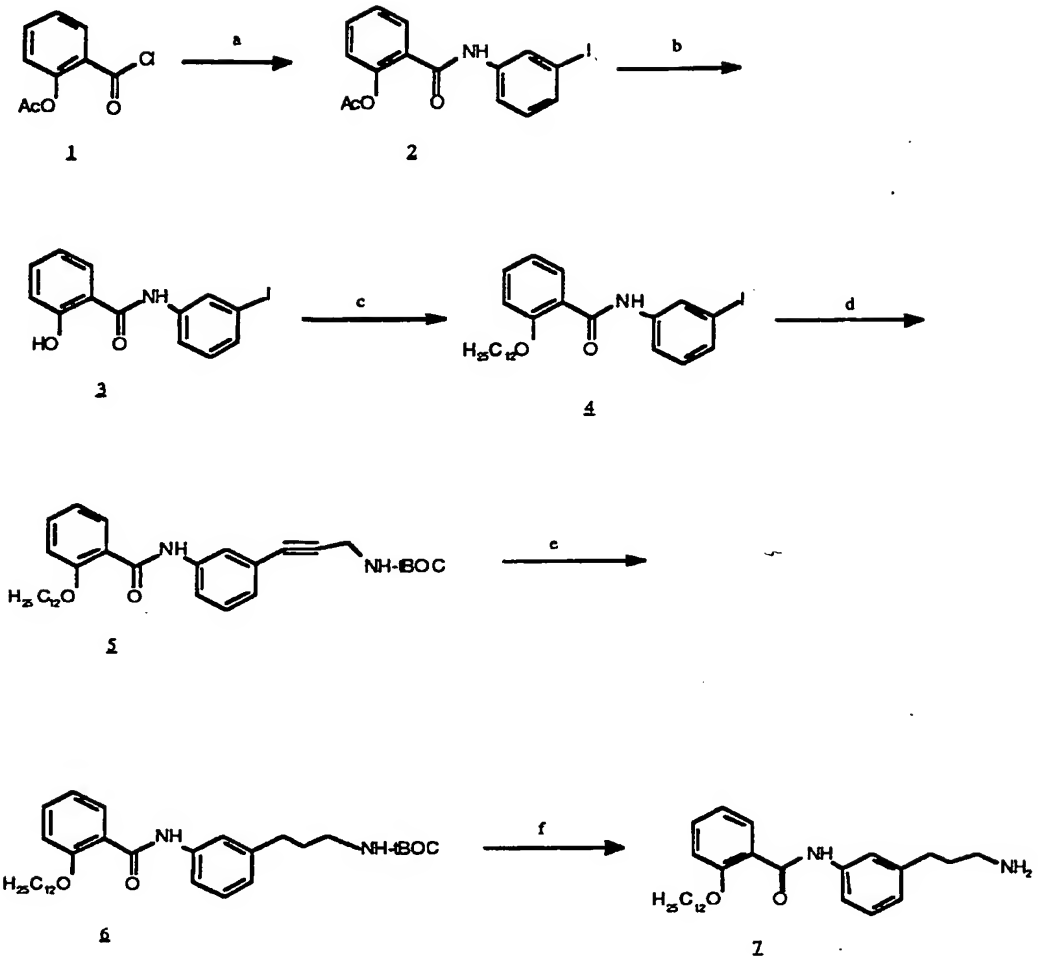
Sch m 12 (Example 18)



a) HCl • $H_2N(CH_2)_6NHBoc$, EDC, HOBT, NMM, CH_2Cl_2; b) $C_{12}H_{25}I$, Cs_2CO_3, DMF, 85 °C; c) $CHCCH_2NHBoc$, 5% $Cl_2Pd(PPh_3)_2$, 5% CuI, Et_3N, 50 °C; d) 10% Pd/C, H_2, MeOH-EtOAc; e) 4N HCl, dioxane.

Scheme 12 illustrates the preparation of a specific compound of formula (II) wherein $-Y(CH_2)_nR^1$ is $-OC_{12}H_{25}$; R^2 is hydrogen; R^3 is $-(CH_2)_kR^6$, wherein k is 3 and R^6 is $-NR^7R^8$, wherein R^7 and R^8, independently from one another, are hydrogen; X is CH; E is $-CH-R^9$, wherein R^9 is hydrogen; Z is $-CH_2$; m is 4; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention.

Scheme 13:

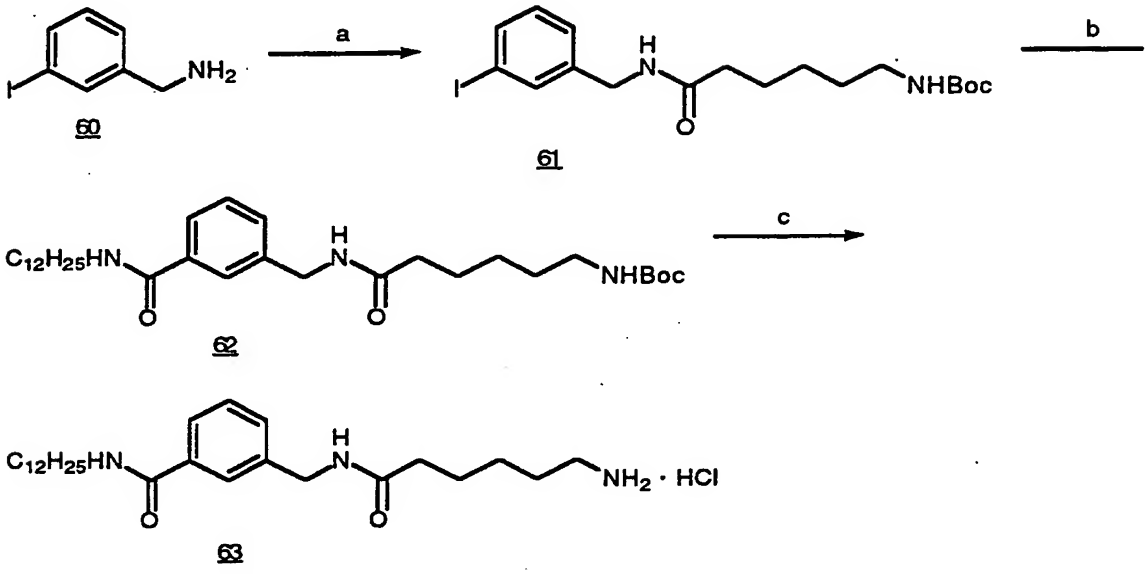


a) pyridine, 3-iodoaniline; b) K_2CO_3, MeOH; c) K_2CO_3, DMF, $C_{12}H_{25}I$; d) $(Ph_3P)_2PdCl_2$, CuI, Et_3N, $\equiv CH_2NH$-tBOC
e) 10% Pd/C, MeOH, H_2; f) HCl.

Scheme 13 illustrates the preparation of a specific compound of formula (II) wherein $-Y(CH_2)_nR^1$ is $-OC_{12}H_{25}$; R^2 is hydrogen; R^3 is hydrogen; X is CH; Z is phenyl; m is 3; p is 0; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention, for example, 3-iodoaniline may be substituted for 2-

iodoaniline as a reagent in step a of Scheme 13, in order to give a compound of the invention with a varying substitution pattern.

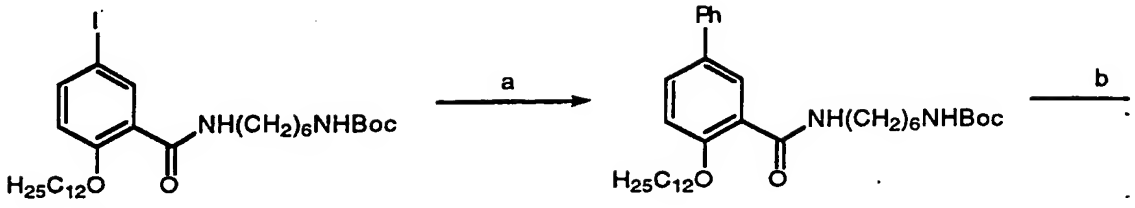
Scheme14 (Example 21)



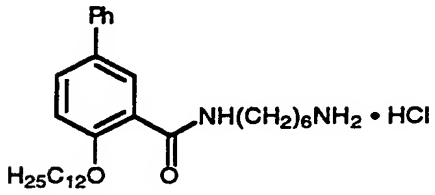
a) (tert-Butoxycarbonyl)-ε-aminocaproic acid, EDC, HOBT, NMM, CH_2Cl_2; b) 5% $Pd(OAc)_2$, 5% dppp, $C_{12}H_{25}NH_2$, Et_3N, DMSO, 70°C; c) 4N HCl/dioxane

Scheme 14 illustrates the preparation of a specific compound of formula (I) wherein $-Y(CH_2)_nR^1$ is $-C(O)NHC_{11}H_{22}CH_3$; R^2 is hydrogen; R^3 is hydrogen; X is CH; Z is $-CH_2$; m is 4; p is 0; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention in order to give a compound of the invention with a varying substitution pattern.

Scheme15 (Exampl 22)



56 (Scheme 12) 64



65

a) 5% $Pd(OAc)_2$, 5% dppb, $PhB(OH)_2$, Na_2CO_3, H_2O, DME, 70-100°C; b) 4N HCl/dioxane.

Scheme 15 illustrates the preparation of a specific compound of formula (II) wherein $-Y(CH_2)_nR^1$ is $-OC_{12}H_{25}$; R^2 is hydrogen; R^3 is phenyl; X is CH; Z is $-CH_2$; m is 5; p is 0; and R^4 and R^5 are hydrogen. Given this description, one of ordinary skill in the art would know how to make other analogous compounds which are within the scope of this invention in order to give a compound of the invention with a varying substitution pattern.

Methods of Treatment and Formulation of Pharmaceutical Compositions

The compounds of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated Protein Kinase C production by such mammal's cells.

Compounds of formula (I) or formula (II) are capable of inhibiting Protein Kinase C isozymes, such as, but not limited to, PKC-α or PKC-ζ. Protein Kinase C isozymes affect a wide variety of cells and tissues and therefore, are important and critical mediators of a wide variety of disease states and conditions. The inhibition of these kinases is of benefit in controlling, reducing and alleviating many of these disease states.

Accordingly, the present invention provides a method of treating a PKC-mediated disease which comprises administering an effective PKC-inhibiting amount of a compound of formula (I) or formula(II) or a pharmaceutically acceptable salt thereof.

In particular, compounds of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof are of use in the prophylaxis or therapy of any disease state in a human, or other mammal, which is exacerbated by or caused by excessive or unregulated PKC production by such mammal's cells.

Accordingly, in another aspect, this invention relates to a method of inhibiting the production of PKC in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated PKC production is implicated in exacerbating and/or causing the disease. These include chronic inflammatory diseases, for example, as described in the following documents; *Scrip No. 1872* (Nov 12 1993), p. 15.; Ohmori et al., (1988) *Arzneim-Forsch./Drug Res.38* (1): pp. 809-814; and Nixon et al., (1991) *Drugs Exp. Clin. Res. 17*: pp. 389-393. and proliferative diseases such as psoriasis, neurological disorders, for example, as described in the following documents; Favaron et al., (1988) *Proc Natl Acad Sci USA 85*: pp. 7351-7355; and Kharlamov A, et al., (1993) *J Neurosci. 13*: p. 2483; and cancer, for example, as described in the following documents; Akinaga et al, (1993) *J. Antibiotics 46*: pp. 1767-1771; Caravatti et al., (1994) *Bioorg. & Med. Chem. Lett. 4*: pp. 399-404; and Meyer et al., (1989) *Int. J. Cancer 43*: pp. 851-856; Schwartz et al., (1993) *Proc. Amer. Assn. Cancer Res.* Abstr. 3471.

The compounds of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof may also be used topically in the treatment or prophylaxis of topical disease states mediated by or exacerbated by excessive PKC production, such as inflamed joints, psoriasis and other conditions associated with inflammation.

The discovery that the compounds of formula (I) and formula (II) are inhibitors of PKC is based upon the effects of the compounds of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof on the action or activity of the PKC enzyme in *in vitro* assays which are described herein.

In order to use a compound of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

The pharmaceutically effective compounds of this invention are administered in conventional dosage forms prepared by combining a compound of formula (I) or (II) ("active ingredient") in an amount sufficient to produce inhibiting activity with standard pharmaceutical carriers or diluents according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1 g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The compounds of formula (I) or formula (II) may also be administered topically to a mammal in need of the inhibition of PKC. Thus, the compounds of formula (I) or formula (II) may be administered topically in the treatment or prophylaxis of inflammation in a mammal, including humans, and may be used in the relief or prophylaxis of PKC mediated diseases.

The amount of a compound of formula (I) or formula (II) required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the inflammatory condition and the mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable anti-inflammatory dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of a compound of formula (I) or formula (II) externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from

1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous or alcoholic solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol. The formulation

may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

The compounds of formula (I) or formula (II) may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage amount of a compound of formula (I) or formula (II) administered by inhalation is from about 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

This invention relates to a method of treating a disease state which is mediated by PKC in a mammal in need thereof, including humans, which comprises administering to such mammal an effective, PKC inhibiting amount of a formula (I) or formula (II) compound.

By the term "treating" is meant either prophylactic or therapeutic therapy. By the term "mediated" is meant caused by or exacerbated by. Such formula (I) or formula (II) compound can be administered to such mammal in a conventional dosage form prepared by combining the formula (I) or formula (II) compound with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The formula (I) or formula (II) compound is administered to a mammal in need of inhibition of PKC in an amount sufficient to inhibit PKC. The route of administration may be oral, parenteral, by inhalation or topical.

The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day for treatment of PKC mediated disease states.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) or formula (II) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the formula (I) or formula (II)

compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

EXAMPLES:

Example 1: Preparation of (*R*)-2,6-diamino-N-[[2-dodecyloxy)phenyl]methyl]-N-methylhexanamide dihydrochloride

a) 2-Dodecyloxybenzaldehyde

A solution of 2-hydroxybenzaldehyde (2.5 g, 20.5 mmol) in DMF (41 mL) was treated with 1-iododododecane (5.48 g, 18.5 mmol) and potassium carbonate (12.77 g, 92.5 mmol) under an argon atmosphere. The reaction was stirred at 90°C for 4 h. The reaction mixture was diluted with ethyl acetate and washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting crude oil was purified by flash column chromatography (silica, 25% ethyl acetate / hexane) to afford the title compound as a crystalline solid. ^1H NMR (400 MHz, $CDCl_3$) 10.52 (s, 1H), 7.82 (d, J = 7.76 Hz, 1H), 7.52 (m, 1H), 6.98 (m, 2H), 4.06 (t, J = 6.52 Hz, 2H), 1.84 (m, 2H), 1.48 (m, 2H), 1.27-1.50 (m, 16H), 0.88 (t, J = 6.11 Hz, 3H).

b) (2-Dodecyloxy)-N-methylbenzylamine

The compound of Example 1(a) (500 mg, 1.72 mmol) was dissolved in methanol (3.6 mL) and treated with methylamine hydrochloride (348 mg, 5.16 mmol), sodium cyanoborohydride (220 mg, 3.44 mmol), and sodium acetate (423 mg, 5.16 mmol). The reaction was stirred at room temperature for 20 h by which time TLC showed complete reaction. Concentrated HCl (to pH 2) was added, and the solution was basified to pH 12 (solid NaOH) after gas evolution stopped. After removing the methanol at reduced pressure, the basic aqueous layer was extracted with diethyl ether (2x). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting crude oil was purified by flash column chromatography (silica, 10% methanol / methylene chloride) to afford the title compound (314 mg, 60%) as an orange oil. MS (ES) m/e 306.2 $[M+H]^+$.

c) (*R*)-2,6-(Di-tert-butoxycarbonyl)diamino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylhexanamide

To a stirred solution of the compound of Example 1(b) (313 mg, 1.03 mmol) in methylene chloride (1.1 mL) was added 4-methylmorpholine (104 mg, 1.03 mmol). The reaction mixture was stirred for 10 minutes and Nα,Nε-di-tert-butoxycarbonyl-L-lysine N-hydroxysuccinimide ester (546 mg, 1.23 mmol) was added followed by 1-hydroxy-benzotriazole hydrate (144 mg, 1.07 mmol). The orange mixture was stirred for 18 h and quenched with N,N-dimethylethylenediamine (27.4 mg, 0.31 mmol). After stirring for 45 minutes, the reaction mixture was diluted with ethyl acetate and washed sequentially with

water, 10% aqueous citric acid, saturated $NaHCO_3$, water, and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed at reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 50% ethyl acetate / hexane) to provide 530 mg (82%) of the title compound as a viscous colorless oil. MS (ES) m/e 634.4 $[M+H]^+$.

d) (*R*)-2,6-Diamino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylhexanamide

To a stirred solution of the compound of Example 1(c) (531 mg, 0.84 mmol) in methylene chloride (1.3 mL) was added 0.41 mL of trifluoroacetic acid. The reaction mixture was stirred for 18 h and the solvent was removed at reduced pressure. The resulting residue was dissolved in aqueous 1 N NaOH and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, 90:1:0.5 chloroform-methanol-ammonium hydroxide) to afford 278 mg (77%) of the title compound as a viscous orange oil. MS (ES) m/e 434.6 $[M+H]^+$, 275.2, 160.

e) (*R*)-2,6-Diamino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylhexanamide dihydrochloride

To a rapidly stirred solution of the compound of Example 1(d) (109 mg, 0.25 mmol) in diethyl ether was added 0.5 mL (0.487 mmol) of 1.0 N HCl in diethyl ether. The reaction mixture was stirred for 5 minutes and the solvent was removed at reduced pressure. The resulting white solid was dissolved in water (HPLC grade) and lyophilized to afford 132 mg (99%) of the title compound as a white amorphous solid. Anal. ($C_{26}H_{49}O_2N_3Cl_2 \cdot 1.5\ H_2O$) calcd: C, 58.52; H, 9.82; N, 7.87. Found C, 58.49; H, 9.80; N, 7.80.

Example 2: Preparation of 6-amino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylhexanamide hydrochloride

a) 6-(tert-Butoxycarbonyl)amino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylhexanamide

To a stirred solution of the compound of Example 1(b) (317 mg, 1.04 mmol) in methylene chloride (1.1 mL) was added 4-methylmorpholine (105 mg, 1.04 mmol). The reaction mixture was stirred for 10 minutes and (tert-butoxycarbonyl)-ε-aminocaproic acid (289 mg, 1.25 mmol) was added followed by 1-hydroxybenzotriazole hydrate (147 mg, 1.08 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride ("EDC") (221 mg, 1.14 mmol). The orange mixture was stirred for 14 h and quenched with N,N-dimethylethylenediamine (27.4 mg, 0.31 mmol). After stirring for 45 minutes, the reaction mixture was diluted with ethyl acetate and washed sequentially with water, 10% aqueous citric acid, saturated $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4 and the solvent was removed at reduced pressure. The resulting crude oil

was purified by flash column chromatography (silica, 35% ethyl acetate / hexane) to provide 468 mg (89%) of the title compound as a viscous colorless oil. MS (ES) m/e 519.4 $[M+H]^+$, 463.4, 419.2.

b) 6-Amino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylhexanamide

A solution of the compound of Example 2(a) in 4N HCl in dioxane (1.1 mL) was stirred for 20 h at room temperature. The solvent was removed at reduced pressure and the residue was dissolved in aqueous 1N NaOH. The aqueous layer was extracted with diethyl ether (2x) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, 50% methanol / chloroform) to afford 133 mg (71%) of the title compound as a viscous oil. MS (ES) m/e 419.4 $[M+H]^+$.

c) 6-Amino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylhexanamide hydrochloride

Following the procedure of Example 1(e), except substituting the compound of Example 2(b) (133 mg, 0.32 mmol) for (*R*)-2,6-diamino-N-[[2-(dodecyloxy)phenyl]-methyl]-N-methylhexanamide, the title compound (153 mg, > 99%) was prepared as a milky oil. Anal. ($C_{26}H_{47}O_2N_2Cl \cdot 0.5\ H_2O$) calcd: C, 67.28; H, 10.42; N, 6.04. Found: C, 67.04; H, 10.29; N, 6.00.

Example 3: Preparation of 6-amino-N-methyl-N-[[[2-(8-phenyl)octyloxy]phenyl]methyl]hexanamide hydrochloride

a) N-Methyl-[2-(8-phenyl)octyloxy]benzylamine

Following the procedures of Example 1(a) and 1(b) respectively, except substituting (8-phenyl)octyl bromide for 1-iodododecane, the title compound was prepared as a pale yellow oil. MS (ES) m/e 326.2 $[M+H]^+$.

b) 6-(tert-Butoxycarbonyl)amino-N-methyl-N-[[[2-(8-phenyl)octyloxy]phenyl]methyl] hexanamide

Following the procedure of Example 2(a), except substituting the compound of Example 3(a) (329 mg, 1.01 mmol) for (2-dodecyloxy)-N-methylbenzylamine, the title compound (453.4 mg, 84%) was prepared as a colorless oil. MS (ES) m/e 539.4 $[M+H]^+$.

c) 6-Amino-N-methyl-N-[[[2-(8-phenyl)octyloxy]phenyl]methyl]hexanamide hydrochloride

A solution of the compound of Example 3(b) (444 mg, 0.83 mmol) in 4N HCl in dioxane (2 mL) was stirred at room temperature for 3 h. The solvent was removed at reduced pressure and the resulting crude oil was triturated with diethyl ether (2x). After carefully decanting the solvent, the pale yellow oil was dried at 65°C under vacuum for 18 h to yield 370 mg (94%) of the title compound. Anal. ($C_{28}H_{43}O_2N_2Cl \cdot 1.25\ H_2O$) calcd: C, 67.58; H, 9.22; N, 5.63. Found: C, 67.68; H, 9.01; N, 5.56.

Example 4: Preparation of (*R*)-2,6-diamino-N-methyl-N-[[[2-(8-phenyl)octyloxy]phenyl]methyl] hexanamide dihydrochloride

a) (*R*)-2,6-(Di-tert-butoxycarbonyl)diamino-N-methyl-N-[[[2-(8-phenyl)octyloxylphenyll methyllhexanamide

Following the procedure of Example 1(c), except substituting N-methyl-[2-(8-phenyl)octyloxy]benzylamine (329 mg, 1.01 mmol) for (2-dodecyloxy)-N-methyl-benzylamine, the title compound (607 mg, 92%) was prepared as a pale yellow viscous oil. MS (ES) m/e 654.4 $[M+H]^+$.

b) (*R*)-2,6-Diamino-N-methyl-N-[[[2-(8-phenyl)octyloxylphenyllmethyllhexanamide dihydrochloride

Following the procedure of Example 3(c), except substituting the compound of Example 4(a) (607 mg, 0.93 mmol) for 6-(tert-butoxycarbonyl)amino-N-methyl-N-[[[2-(8-phenyl)octyloxy]phenyl]methyl]hexanamide, the title compound (433 mg, 88%) was prepared as a white powder. Anal. ($C_{28}H_{45}O_2N_3Cl_2 \cdot 0.25\ H_2O$) calcd: C, 63.32; H, 8.63; N, 7.91. Found: C, 63.08; H, 8.65; N, 7.82.

Example 5: Preparation of 6-amino-N-[[2-(hexadecyloxy)phenyl]methyl]-N-methylhexanamide hydrochloride

a) (2-Hexadecyloxy)-N-methylbenzylamine

Following the procedures of Example 1(a) and 1(b) respectively, except substituting 1-iodohexadecane for 1-iodododecane, the title compound was prepared as a white solid. ^1H NMR (400 MHz, $CDCl_3$) 7.37 (d, J = 7.37 Hz, 1H), 7.30 (m, 1H), 6.93 (t, J = 7.52 Hz, 1H), 6.88 (d, J = 8.26 Hz, 1H), 5.85 (br s, 1H), 4.01 (m, 4H), 2.48 (s, 3H), 1.83 (m, 2H), 1.42 (m, 2H), 1.26 (m, 24H), 0.88 (t, J = 6.59 Hz, 3H).

b) 6-(tert-Butoxycarbonyl)amino-N-[[2-(hexadecyloxy)phenyl]methyl]-N-methylhexanamide

Following the procedure of Example 2(a), except substituting the compound of Example 5(a) (151 mg, 0.44 mmol) for (2-dodecyloxy)-N-methylbenzylamine, the title compound (216 mg, 86%) was prepared as a white solid. MS (ES) m/e 575.6 $[M+H]^+$.

c) 6-Amino-N-[[2-(hexadecyloxy)phenyl]methyl]-N-methylhexanamide hydrochloride

A solution of the compound of Example 5(b) (216 mg, 0.38 mmol) in 4N HCl in dioxane (0.93 mL) was stirred at room temperature for 1 h. The solvent was removed at reduced pressure and the resulting residue was triturated with acetonitrile (2x). After carefully decanting the solvent, the resulting oil was dissolved in water (HPLC grade) and lyophilized to afford 165 mg (85%) of the title compound as a white amorphous solid.

Anal. ($C_{30}H_{55}O_2N_2Cl$) calcd: C, 70.48; H, 10.84; N, 5.48. Found: C, 70.42; H, 10.87; N, 5.87.

Example 6: Preparation of 4-amino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylbutanamide hydrochloride

a) 4-(tert-Butoxycarbonyl)amino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylbutanamide

Following the procedure of Example 2(a), except substituting (tert-butoxycarbonyl)-γ-aminobutyric acid (100 mg, 0.49 mmol) for (tert-butoxycarbonyl)-ε-aminocaproic acid, the title compound (180 mg, 90%) was prepared as a colorless oil. MS (ES) m/e 491.2 $[M+H]^+$.

b) 4-Amino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylbutanamide hydrochloride

Following the procedure of Example 5(c), except substituting the compound of Example 6(a) (180 mg, 0.37 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[2-(hexadecyloxy)phenyl]methyl]-N-methylhexanamide, the title compound (124 mg, 74%) was prepared as a white amorphous solid. Anal. ($C_{24}H_{43}O_2N_2Cl \cdot 0.125\ H_2O$) calcd: C, 67.14; H, 10.21; N, 6.52. Found: C, 67.07; H, 10.16; N, 6.59.

Example 7: Preparation of 6-amino-N-[[3-(dodecyloxy)phenyl]methyl]-N-methylhexanamide hydrochloride

a) (3-Dodecyloxy)-N-methylbenzylamine

Following the procedures of Example 1(a) and 1(b) respectively, except substituting 3-hydroxybenzaldehyde for 2-hydroxybenzaldehyde, the title compound was prepared as a white solid. MS (ES) m/e 306.2 $[M+H]^+$.

b) 6-(tert-Butoxycarbonyl)amino-N-[[3-(dodecyloxy)phenyl]methyl]-N-methylhexanamide

Following the procedure of Example 2(a), except substituting the compound of Example 7(a) (128 mg, 0.42 mmol) for (2-dodecyloxy)-N-methylbenzylamine, the title compound (174 mg, 80%) was prepared as a colorless oil. MS (ES) m/e 519.2 $[M+H]^+$, 463.2, 419.2.

c) 6-Amino-N-[[3-(dodecyloxy)phenyl]methyl]-N-methylhexanamide hydrochloride

Following the procedure of Example 5(c), except substituting the compound of Example 7(b) (174 mg, 0.34 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[2-(hexadecyloxy)phenyl]methyl]-N-methylhexanamide, the title compound (155 mg, >99%) was prepared as a white amorphous solid. Anal. ($C_{26}H_{47}O_2N_2Cl$) calcd: C, 68.62; H, 10.41; N, 6.16. Found: C, 68.37; H, 10.40; N, 6.19.

Example 8: Preparation of N-[[2-(dodecyloxy)phenyl]methyl]-N-methyl-6-morpholinohexanamide

a) 6-Bromo-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylhexanamide

To a stirred solution of the compound of Example 1(b) (131 mg, 0.43 mmol) in methylene chloride (2.1 mL) at 0°C under an argon atmosphere was added 6-bromohexanoyl chloride (96.4 mg, 0.52 mmol). After 30 minutes, the reaction was quenched with saturated $NaHCO_3$ and diluted with ethyl acetate. The organic layer was washed with water and brine, dried($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, 50% ethyl acetate / hexane) to provide 142 mg (73%) of the title compound as a colorless oil. MS (ES) m/e 482.2 $[M+H]^+$.

b) N-[[2-(Dodecyloxy)phenyl]methyl]-N-methyl-6-morpholinohexanamide

To a solution of the compound of Example 8(a) (46 mg, 0.103 mmol) in N,N-dimethylformamide (2 mL) under an argon atmosphere was added morpholine (0.022 mL) and a catalytic amount of sodium iodide (1 mg, 0.007 mmol). The reaction was stirred for 16 h and the solvent was removed at reduced pressure. The residue was poured into water and the aqueous layer was extracted with ethyl ether (2x). The combined organic extracts were washed sequentially with saturated $NaHCO_3$, water, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, 10% methanol / methylene chloride) to afford 217 mg (91%) of the title compound as a colorless oil. Anal. ($C_{30}H_{52}O_3N_2 \cdot 0.67\ H_2O$) calcd: C, 71.96; H, 10.74; N, 5.59. Found: C, 72.05; H, 10.41; N, 5.69.

Example 9: Preparation of N-[[2-(dodecyloxy)phenyl]methyl]-N-[methylhexanamidol-6-N′, N′, N′-trimethylammonium bromide

a) N-[[2-(Dodecyloxy)phenyl]methyl]-N-[methylhexanamidol-6-N′, N′, N′-trimethylammonium bromide

Trimethyl amine gas was bubbled through a stirred solution of the compound of Example 8(a) (144 mg, 0.30 mmol) in N,N-dimethylformamide (10 mL) under an argon atmosphere for 5 minutes. The reaction was stirred for 18 h at room temperature and the solvent was removed at reduced pressure. The resulting residue was triturated with acetonitrile (2x) and lyophilized to provide 150 mg (93%) of the title compound as a hygroscopic white solid. Anal. ($C_{29}H_{53}O_2N_2Br \cdot 0.33\ H_2O$) calcd: C, 63.60; H, 9.88; N, 5.11. Found: C, 63.36; H, 9.83; N, 5.17.

Example 10: Preparation of 6-amino-N-methyl-N-[[[2-(8-phenyl)octyl]phenyl]methyl]hexanamide hydrochloride

a) N-Methyl-[2-(8-phenyl)octyl]benzylamine

Following the procedures of Example 1(a) and 1(b) respectively, except substituting 2-(8-phenyl)octylbenzaldehyde for 2-hydroxybenzaldehyde, the title compound was prepared as a pale yellow oil. MS (ES) m/e 310.2 $[M+H]^+$, 279.

b) 6-(tert-Butoxycarbonyl)amino-N-methyl-N-[[[2-(8-phenyl)octyl]phenyl]methyl] hexanamide

Following the procedure of Example 2(a), except substituting the compound of Example 10(a) (687 mg, 2.22 mmol) for (2-dodecyloxy)-N-methylbenzylamine, the title compound (973 mg, 84%) was prepared as a yellow oil. MS (ES) m/e 523.4 $[M+H]^+$, 423.4.

c) 6-Amino-N-methyl-N-[[[2-(8-phenyl)octyl]phenyl]methyl]hexanamide hydrochloride

Following the procedure of Example 3(c), except substituting the compound of Example 10(b) (174 mg, 0.34 mmol) for 6-(tert-butoxycarbonyl)amino-N-methyl-N-[[[2-(8-phenyl)octyloxy]phenyl]methyl]hexanamide, the title compound (747 mg, 88%) was prepared as a pale yellow oil. Anal. ($C_{28}H_{43}ON_2Cl \cdot H_2O$) calcd: C, 70.49; H, 9.51; N, 5.87. Found: C, 70.33; H, 9.17; N, 5.75.

Example 11: Preparation of N-[[(5-amino-2-dodecyloxy)phenyl]methyl]-6-amino-N-methylhexanamide dihydrochloride

a) (2-Dodecyloxy-5-nitro)-N-methylbenzylamine

Following the procedures of Example 1(a) and 1(b) respectively, except substituting 2-hydroxy-5-nitrobenzaldehyde for 2-hydroxybenzaldehyde, the title compound was prepared as a white solid. MS (ES) m/e 351.2 $[M+H]^+$.

b) 6-(tert-Butoxycarbonyl)amino-N-[[(2-dodecyloxy-5-nitro)phenyl]methyl]-N-methyl-hexanamide

Following the procedure of Example 2(a), except substituting the compound of Example 11(a) (227 mg, 0.65 mmol) for (2-dodecyloxy)-N-methylbenzylamine, the title compound (303 mg, 83%) was prepared as an off-white solid. MS (ES) m/e 564.4 $[M+H]^+$, 508.4, 464.4.

c) N-[[(5-Amino-2-dodecyloxy)phenyl]methyl]-6-(tert-butoxycarbonyl)amino-N-methylhexanamide

10% Palladium on activated carbon (30 mg) was added to a solution of the compound of Example 11(b) (303 mg, 0.54 mmol) in methanol (0.6 mL) and ethyl acetate (0.6 mL) under an argon atmosphere. The reaction was stirred under an hydrogen atmosphere (balloon pressure) for 3 h. The reaction mixture was diluted with methylene chloride and filtered through Celite®. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (silica, 10% methanol / methylene chloride), affording

272 mg (95%) of the title compound as a rose-colored oil. MS (ES) m/e 534.4 $[M+H]^+$, 434.2.

d) N-[[(5-Amino-2-dodecyloxy)phenyl]methyl]-6-amino-N-methylhexanamide dihydrochloride

Following the procedure of Example 5(c), except substituting the compound of Example 11(c) (127 mg, 0.24 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[2-(hexadecyl-oxy)phenyl]methyl]-N-methylhexanamide and diethyl ether for acetonitrile as the trituration solvent, the title compound (141 mg, >99%) was prepared as a white amorphous solid. Anal. ($C_{26}H_{49}O_2N_3Cl_2 \cdot 0.25\ H_2O$) calcd: C, 61.10; H, 9.76; N, 8.22. Found: C, 61.11; H, 9.70; N, 7.88.

Example 12: Preparation of 6-amino-N-[[2-dodecyloxy-5-[(1-oxooctyl)amino]phenyl]methyl]-N-methylhexanamide hydrochloride

a) 6-(tert-Butoxycarbonyl)amino-N-[[2-dodecyloxy-5-[(1-oxooctyl)amino]phenyl]-methyl]-N-methylhexanamide

Following the procedure of Example 8(a), except substituting the compound of Example 11(c) (152 mg, 0.29 mmol) for (2-dodecyloxy)-N-methylbenzylamine and octanoyl chloride for 6-bromo-hexanoyl chloride, the title compound (144 mg, 81%) was prepared. MS (ES) m/e 660.4 $[M+H]^+$, 560.4.

b) 6-Amino-N-[[2-dodecyloxy-5-[(1-oxooctyl)amino]phenyl]methyl]-N-methylhexanamide hydrochloride

Following the procedure of Example 5(c), except substituting the compound of Example 12(a) (145 mg, 0.27 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[2-(hexadecyl-oxy)phenyl]methyl]-N-methylhexanamide, the title compound (113 mg, 87%) was prepared as a pale yellow oil. Anal. ($C_{34}H_{62}O_3N_3Cl \cdot 0.125\ H_2O$) calcd: C, 68.22; H, 10.48; N, 7.02. Found: C, 68.07; H, 10.46; N, 6.73.

Example 13: Preparation of 6-amino-N-[[2-(dodecyloxy)phenyl]methyl]hexanamide hydrochloride

a) 2-Dodecyloxybenzamide

Following the procedure of Example 1(a), except substituting 2-hydroxy-benzamide for 2-hydroxybenzaldehyde, the title compound was prepared as a white crystalline solid. MS (ES) m/e 306 $[M+H]^+$.

b) (2-Dodecyloxy)benzylamine

To a stirred solution of the compound of Example 13(a) (100 mg, 0.33 mmol) in tetrahydrofuran (1.5 mL) at 0°C under an argon atmosphere was added a solution of 0.1 M lithium aluminum hydride in tetrahydrofuran (0.66 mL, 0.66 mmol). The reaction was

stirred at room temperature for 1 h and then heated at 75°C for 2.5 h. The reaction mixture was cooled to room temperature and the excess lithium aluminum hydride was destroyed by slowly adding ethyl acetate. A concentrated solution of sodium hydroxide was slowly added until white solids formed. The mixture was diluted with diethyl ether and filtered. The solvent was removed at reduced pressure from the filtrate, and the white residue was purified by flash column chromatography (silica, 90:10:1 methylene chloride-methanol-water) to afford 48 mg (50%) of the title compound as a yellow oil. MS (ES) m/e 292.2 $[M+H]^+$, 275.2.

c) 6-(tert-Butoxycarbonyl)amino-N-[[2-(dodecyloxy)phenyl]methyl]hexanamide

Following the procedure of Example 2(a), except substituting the compound of Example 13(b) (127 mg, 0.44 mmol) for (2-dodecyloxy)-N-methylbenzylamine, the title compound (186 mg, 80%) was prepared as a white solid. MS (ES) m/e 505.2 $[M+H]^+$.

d) 6-Amino-N-[[2-(dodecyloxy)phenyl]methyl]hexanamide hydrochloride

Following the procedure of Example 5(c), except substituting the compound of Example 13(c) (187 mg, 0.35 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[2-(hexadecyloxy)phenyl]methyl]-N-methylhexanamide, the title compound (151 mg, 98%) was prepared as a white amorphous solid. Anal. ($C_{25}H_{45}O_2N_2Cl \cdot 0.125\ H_2O$) calcd: C, 67.73; H, 10.29; N, 6.32. Found: C, 67.71; H, 10.31; N, 6.62.

Example 14: Preparation of 6-amino-N-[(3-dodecyloxy)-2-pyridinyl]methyl]-N-methylhexanamide dihydrochloride

a) 3-Dodecyloxy-2-(hydroxymethyl)pyridine

Following the procedure of Example 1(a), except substituting 3-hydroxy-2-(hydroxymethyl)pyridine hydrochloride (250 mg, 1.55 mmol) for 2-hydroxybenzaldehyde, the title compound (277 mg, 64%) was prepared as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) 8.12 (d, J = 4.3 Hz, 1H), 7.20 (m, 1H), 7.10 (m, 1H), 4.34 (br s, 1H), 4.76 (s, 2H), 3.99 (t, J = 6.57 Hz, 2H), 1.81 (m, 2H), 1.46 (m, 2H), 1.28 (m, 16H), 0.88 (t, J = 6.6 Hz, 3H).

b) 2-(3-Dodecyloxy)pyridine carboxaldehyde

A stirred solution of the compound of Example 14(a) (277 mg, 0.99 mmol) in methylene chloride (2 mL) under an argon atmosphere was treated with MnO_2 (430 mg, 4.95 mmol). The reaction was stirred at room temperature for 36 h and filtered through Celite®. The solvent was removed at reduced pressure and the resulting crude oil was purified by flash column chromatography (silica, 2% methanol / methylene chloride) to afford the title compound (213 mg, 77%) as a pale yellow oil. MS (ES) m/e 292.3 $[M+H]^+$.

c) N-[(3-Dodecyloxy)-2-pyridinyl]methyl]-N-methylamine

Following the procedure of Example 1(b), except substituting the compound of Example 14(b) (213 mg, 0.73 mmol) for 2-dodecyloxybenzaldehyde, the title compound (151 mg, 67%) was prepared. MS (ES) m/e 307.2 $[M+H]^+$.

d) 6-(tert-Butoxycarbonyl)amino-N-[(3-dodecyloxy)-2-pyridinyl]methyl]-N-methyl-hexanamide

Following the procedure of Example of 2(b), except substituting the compound of 14(c) (151 mg, 0.49 mmol) for (2-dodecyloxy)-N-methylbenzylamine, the title compound (228 mg, 90%) was prepared as a yellow solid. MS (ES) m/e 519.4 $[M+H]^+$, 420.2.

e) 6-Amino-N-[(3-dodecyloxy)-2-pyridinyl]methyl]-N-methylhexanamide dihydrochloride

Following the procedure of Example 5(c), except substituting the compound of Example 14(d) (228 mg, 0.45 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[2-(hexadecyloxy)phenyl]methyl]-N-methylhexanamide, the title compound (199 mg, 90%) was prepared as a hygroscopic pale yellow solid. Anal. ($C_{25}H_{47}O_2N_3Cl_2 \cdot 0.67\ H_2O$) calcd: C, 59.51; H, 9.65; N, 8.33. Found: C, 59.19; H, 9.68; N, 8.40.

Example 15: Preparation of N-(6-aminohexane-1-yl)-2-dodecyloxybenzamide trifluoroacetate.

a) N-[6-(tert-Butoxycarbonylamino)hexane-1-yl]-2-dodecyloxybenzamide

N-Boc-1, 6-diaminohexane hydrochloride (255 mg, 1.01 mmol, Fluka) was dissolved in dry pyridine (2 mL) and treated with acetylsalicyloyl chloride (200 mg, 1.01 mmol). The reaction was stirred under an argon atmosphere at room temperature for 4 h. The reaction was diluted with CH_2Cl_2 and poured into 10% HCl. The product was extracted into CH_2Cl_2 and the combined organic extracts were washed with $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of the solvent gave crude product which was used directly in the next step.

The compound prepared above was dissolved in MeOH (5 mL) and treated with an excess of K_2CO_3. The reaction was vigorously stirred for 45 minutes at room temperature under an argon atmosphere. The reaction solution was poured into aqueous NH_4Cl and the product extracted into CH_2Cl_2. The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave a colorless oil which was used directly in the next step.

The crude product from above was dissolved in DMF (1 mL) and treated with 1-iodododecane (0.25 mL, 1.01 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred under Ar for 30 minutes at 85 °C. After cooling, the reaction was diluted with EtOAc and washed with H_2O and brine and dried ($MgSO_4$). The product was purified by flash column chromatography (silica, 30% EtOAc in hexane) to give 321 mg (64%, 3 steps) as a white solid. Melting point 70-73°C; MS (ES+) m/e 505.2 $[M+H]^+$.

b) N-(6-Aminohexane-1-yl)-2-dodecyloxybenzamide, trifluoroacetate

The compound from Example 15(a) (300 mg, 0.60 mmol) was dissolved in dry CH_2Cl_2 (2.4 mL) and treated with trifluoroacetic acid (TFA, 0.60 mL). The reaction was stirred under Ar at 0 °C for 2 h followed by 30 minutes at room temperature. The solvent and excess TFA were evaporated and the resulting oil was dissolved in H_2O. Lyophilization provided the desired product as a light tan amorphous solid (320 mg, 100%). MS (DCI) m/e 405.5 $[M+H]^+$, free base; 306.3 $[M-(CH_2)_6NH_2+.H]^+$.

Example 16: Preparation of N-(6-aminohexan-1-yl)-2-dodecyloxy-5-(2-methoxycarbonyl)ethylbenzamide hydrochloride

a) N-[6-(tert-Butoxycarbonyl)aminohexan-1-yl]-5-formyl-2-hydroxybenzamide

Following the procedure of Example 2(a), except substituting 5-formylsalicylic acid (500 mg, 3 mmol) for (tert-butoxycarbonyl)-ε-aminocaproic acid and N-(tert-butoxycarbonyl)-1,6-diaminohexane dihydrochloride (910 mg, 3.6 mmol) for (2-dodecyloxy)-N-benzylamine, the title compound (426 mg, 72%) was prepared as a white solid. MS (ES) m/e 365.2 $[M+H]^+$.

b) N-[6-(tert-Butoxycarbonyl)aminohexan-1-yl]-2-dodecyloxy-5-formylbenzamide

Following the procedure of Example 1(a), except substituting the compound of Example 16(a) (254 mg, 0.70 mmol) for 2-hydroxybenzaldehyde and cesium carbonate for potassium carbonate, the title compound (328 mg, 88%) was prepared as a white solid. MS (ES) m/e 533.2 $[M+H]^+$.

c) N-[6-(tert-Butoxycarbonyl)aminohexan-1-yl]-2-dodecyloxy-5-[E-(2-methoxycarbonyl)vinylbenzamide

A stirred solution of the compound of Example 16(b) (328 mg, 0.62 mmol) in toluene (2 mL) was treated with methyl (triphenylphosphoranylidene)acetate (231 mg, 0.69 mmol) and heated at 50°C for 1 h. The solvent was removed at reduced pressure and the resulting residue was purified by flash column chromatography (silica, 40:40:20 ethyl acetate-hexane-methylene chloride) to afford the title compound (327 mg, 90%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.94 (m, 1H), 7.67 (d, J = 16 Hz, 1H), 7.55 (s, 1H), 6.97 (m, 1H), 6.42 (d, J = 16 Hz, 1H), 4.57 (br s, 1H), 4.15 (t, J = 6.4 Hz, 2H), 3.80 (s, 3H), 3.46 (q, J = 6.83 Hz, 2H), 3.11 (m, 2H), 1.91 (m, 2H), 1.61 (m, 2H), 1.43 (m, 33H), 0.88 (t, J = 6.55 Hz, 3H).

d) N-[6-(tert-Butoxycarbonyl)aminohexan-1-yl]-2-dodecyloxy-5-(2-methoxycarbonyl)-ethylbenzamide

Following the procedure of Example 11(c), except substituting the compound of Example 16(c) (327 mg, 0.56 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[(2-dodecyl-

oxy-5-nitro)phenyl]methyl]-N-methylhexanamide, the title compound (296 mg, 90%) was prepared as a white solid. MS (ES) m/e 591.4 $[M+H]^+$.

e) N-(6-Aminohexan-1-yl)-2-dodecyloxy-5-(2-methoxycarbonyl)ethylbenzamide hydrochloride

Following the procedure of Example 5(c), except substituting the compound of Example 16(d) (197 mg, 0.33 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[2-(hexadecyl-oxy)phenyl]methyl]-N-methylhexanamide and diethyl ether for acetonitrile as the triturating solvent, the title compound (175 mg, 99%) was prepared as an amorphous white solid. Anal. ($C_{29}H_{51}O_4N_2Cl \cdot 0.5\ H_2O$) calcd: C, 64.96; H, 9.77; N, 5.22. Found: C, 65.11; H, 9.82; N, 5.06.

Example 17: Preparation of N-[4-(2-amino)ethyl]phenyl-2-dodecyloxybenzamide hydrochloride

a) N-(tert-Butoxycarbonyl)-4-nitrophenethylamine

A stirred, cooled (-78°C) solution of di-tert-butyl dicarbonate (539 mg, 2.47 mmol) in DMF (1 mL) under an argon atmosphere was treated with a solution of 4-nitro-phenethylamine hydrochloride (500 mg, 2.47 mmol) in DMF (7 mL) and pyridine (0.2 mL, 2.47 mmol). The reaction was allowed to warm slowly to room temperature and stirred for 20 h. The reaction mixture was diluted with ethyl acetate and washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica, 30% ethyl acetate / hexane) to afford the title compound (176 mg, 27%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 4.79 (br s, 1H), 3.92 (s, 2H), 2.23 (s, 1H), 1.45 (s, 9H).

b) N-(tert-Butoxycarbonyl)-4-aminophenethylamine

Following the procedure of Example 11(c), except substituting the compound of Example 17(a) (176 mg, 0.66 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[(2-dodecyl-oxy-5-nitro)phenyl]methyl]-N-methylhexanamide, the title compound (130 mg, 83%) was prepared as a pink crystalline solid. MS (ES) m/e 237.0 $[M+H]^+$.

c) N-[(tert-Butoxycarbonyl)-4-(2-amino)ethyl]phenyl-2-hydroxybenzamide

Following the procedure of Example 2(a), except substituting salicylic acid (64 mg, 0.46 mmol) for (tert-butoxycarbonyl)-ε-aminocaproic acid and the compound of Example 17(b) (130 mg, 0.55 mmol) for (2-dodecyloxy)-N-benzylamine, the title compound (116 mg, 71%) was prepared as a white solid. MS (ES) m/e 357.2 $[M+H]^+$.

d) N-[(tert-Butoxycarbonyl)-4-(2-amino)ethyl]phenyl-2-dodecyloxybenzamide

Following the procedure of Example 1(a), except substituting the compound of Example 17(c) for 2-hydroxybenzaldehyde and cesium carbonate for potassium carbonate, the title compound was prepared as a white solid. MS (ES) m/e 525.2 $[M+H]^+$.

e) N-[4-(2-Amino)ethyl]phenyl-2-dodecyloxybenzamide hydrochloride

Following the procedure of Example 5(c), except substituting the compound of Example 17(d) (89 mg, 0.17 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[2-(hexadecyl-oxy)phenyl]methyl]-N-methylhexanamide and diethyl ether for acetonitrile as the triturating solvent, the title compound (77 mg, 98%) was prepared as a white amorphous solid. Anal. ($C_{27}H_{41}O_2N_2Cl \cdot 0.25\ H_2O$) calcd: C, 69.65; H, 8.98; N, 6.02. Found: C, 69.87; H, 9.05; N, 5.80.

Example 18: Preparation of N-(6-aminohexan-1-yl)-5-(3-amino)propyl-2-dodecyloxybenzamide dihydrochloride

a) N-(tert-Butoxycarbonyl)-propynylamine

Following the procedure of Example 17(a), except substituting 2-propynylamine (496 mg, 9 mmol) for 4-nitrophenethylamine hydrochloride and methylene chloride for DMF and pyridine, the title compound (1.14 g, 82%) was prepared as a white crystalline solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 6.85 Hz, 2H), 7.36 (d, J = 8.53 Hz, 2H), 4.62 (br s, 1H), 3.42 (m, 2H), 2.93 (t, J = 6.93 Hz, 2H), 1.43 (s, 9H).

b) N-[6-(tert-Butoxycarbonyl)aminohexan-1-yl]-2-hydroxy-5-iodobenzamide

Following the procedure of Example 2(a), except substituting 5-iodosalicylic acid (500 mg, 1.89 mmol) for (tert-butoxycarbonyl)-ε-aminocaproic acid and N-(tert-butoxy-carbonyl)-1,6-diaminohexane dihydrochloride (573 mg, 2.27 mmol) for (2-dodecyloxy)-N-benzylamine, the title compound (465 mg, 53%) was prepared as a white solid. MS (ES) m/e 463.0 $[M+H]^+$.

c) N-[6-(tert-Butoxycarbonyl)aminohexan-1-yl]-2-dodecyloxy-5-iodobenzamide

Following the procedure of Example 1(a), except substituting the compound of Example 18(b) for 2-hydroxybenzaldehyde and cesium carbonate for potassium carbonate, the title compound was prepared as a white solid. MS (ES) m/e 631.2 $[M+H]^+$.

d) N-[6-(tert-Butoxycarbonyl)aminohexan-1-yl]-5-[3-(tert-butoxycarbonyl)amino]-propynyl-2-dodecyloxybenzamide

To a stirred solution of the compound of Example 18(c) (100 mg, 0.16 mmol) in triethylamine (0.4 mL) under an argon atmosphere was added the compound of Example 18(a) (30 mg, 0.19 mmol), bis(triphenylphosphine)palladium(II) chloride (5.58 mg, 0.08 mmol), and copper(I) iodide (1.51 mg, 0.08 mmol). The resulting mixture was heated at 50°C for 4 h. Upon cooling to room temperature, the reaction mixture was diluted with ethyl acetate and washed with 5% HCl, water, and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica, 25% and 40% ethyl acetate / hexane) to afford the title compound (98 mg, 93%) as a dirty yellow solid. MS (ES) m/e 658.4 $[M+H]^+$.

e) N-[6-(tert-Butoxycarbonyl)aminohexan-1-yl]-5-[3-(tert-butoxycarbonyl)amino]-propyl-2-dodecyloxybenzamide

Following the procedure of Example 11(c), except substituting the compound of Example 18(d) (97 mg, 0.15 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[(2-dodecyloxy-5-nitro)phenyl]methyl]-N-methylhexanamide, the title compound (91 mg, 93%) was prepared as a white solid. MS (ES) m/e 662.4 $[M+H]^+$.

f) N-(6-Aminohexan-1-yl)-5-(3-amino)propyl-2-dodecyloxybenzamide dihydrochloride

Following the procedure of Example 5(c), except substituting the compound of Example 18(e) (87 mg, 0.13 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[2-(hexadecyloxy)phenyl]methyl]-N-methylhexanamide and diethyl ether for acetonitrile as the triturating solvent, the title compound (67 mg, 97%) was prepared as a pale pink amorphous solid. Anal. ($C_{28}H_{53}O_2N_3Cl_2 \cdot 1.25\ H_2O$) calcd: C, 60.35; H, 10.04; N, 7.54. Found: C, 60.43; H, 10.07; N, 7.53.

Example 19: Preparation of N-(6-aminohexan-1-yl)-2-dodecyloxy-5-(2-phenylethynyl)benzamide hydrochloride

a) N-[6-(tert-Butoxycarbonyl)aminohexan-1-yl)-2-dodecyloxy-5-(2-phenylethynyl) benzamide

Following the procedure of Example 18(d), except substituting phenylacetylene for N-(tert-butoxycarbonyl)-propynylamine, the title compound was prepared as a yellow solid. MS (ES) m/e 605.4 $[M+H]^+$.

b) N-(6-Aminohexan-1-yl)-2-dodecyloxy-5-(2-phenylethynyl)benzamide hydrochloride

A solution of the compound of Example 19(a) in 4N HCl/dioxane was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the resulting residue was triturated with diethyl ether. After removing the diethyl ether by filtration, the residue was dissolved in methanol and transferred to a round-bottomed flask. The methanol was removed *in vacuo* and the resulting white solid was dissolved in water (HPLC grade) and lyophilized to afford the title compound as an amorphous white solid. Anal. ($C_{33}H_{49}O_2N_2Cl \cdot 0.63\ H_2O$) calcd: C, 71.74; H, 9.17; N, 5.07. Found: C, 71.36; H, 8.85; N, 5.40.

Example 20 : Preparation of N-(6-aminohexan-1-yl)-2-dodecyloxy-5-(2-phenylethyl)benzamide hydrochloride

a) N-[6-(tert-Butoxycarbonyl)aminohexan-1-yl)-2-dodecyloxy-5-(2-phenylethyl) benzamide

Following the procedure of Example 11(c), except substituting the compound of 19 (a) (61.8 mg, 0.1 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[(2-dodecyloxy-5-

nitro)phenyl]methyl]-N-methylhexanamide, the title compound (47 mg, 77%) was prepared as a white solid. MS (ES) m/e 609.4 $[M+H]^+$.

b) N-(6-Aminohexan-1-yl)-2-dodecyloxy-5-(2-phenylethyl)benzamide hydrochloride

Following the procedure of Example 19(b), except substituting the compound of Example 20(a) (47 mg, 0.077 mmol) for N-[6-(tert-butoxycarbonyl)aminohexan-1-yl)-2-dodecyloxy-5-(2-phenylethynyl)benzamide and acetonitrile for diethyl ether as the triturating solvent, the title compound (37 mg, 88%) was prepared as an amorphous white solid. Anal. ($C_{33}H_{53}O_2N_2Cl \cdot 0.5\ H_2O$) calcd: C, 71.52; H, 9.82; N, 5.05. Found: C, 71.70; H, 9.76; N, 4.98.

Example 21: Preparation of 6-amino-N-[[3-[(N-dodecyl)aminocarbonyl]phenyl]methyl]hexanamide hydrochloride

a) 6-(tert-Butoxycarbonyl)amino-N-[[(3-iodo)phenyl]methyl]hexanamide

Following the procedure of Example 2(a), except substituting 3-iodobenzylamine (200 mg, 0.74 mmol) for (2-dodecyloxy)-N-methylbenzylamine, the title compound (301 mg, 91%) was prepared as a white solid. MS (ES) m/e 447 $[M+H]^+$, 391, 347.

b) 6-(tert-Butoxycarbonyl)amino-N-[[3-[(N-dodecyl)aminocarbonyl]phenyl]methyl]-hexanamide

A solution of the compound of Example 21(a) (150 mg, 0.34 mmol) in anhydrous dimethyl sulfoxide (1 mL) was added to palladium acetate (3.8 mg, 5 mmol %), 1,3-bis-(diphenylphosphino)propane (6.9 mg, 5 mmol %), triethylamine (0.1 mL), and dodecylamine (75 mg, 0.4 mmol). The reaction was purged with CO for 5 min and stirred under a CO atmosphere (double-walled balloon) at 70°C for 20 h. The reaction mixture was diluted with ethyl acetate and washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica, 50% ethyl acetate / hexane and 3% methanol in methylene chloride) to afford the title compound (15 mg, 9%) as a white solid. MS (ES) m/e 532.4 $[M+H]^+$.

c) 6-Amino-N-[[3-[(N-dodecyl)aminocarbonyl]phenyl]methyl]hexanamide hydrochloride

Following the procedure of Example 19(b), except substituting the compound of Example 21(b) (15 mg, 0.028 mmol) for N-[6-(tert-butoxycarbonyl)aminohexan-1-yl)-2-dodecyloxy-5-(2-phenylethynyl)benzamide, the title compound (13 mg, 92%) was prepared as an amorphous white solid. Anal. ($C_{26}H_{46}O_2N_3Cl \cdot H_2O$) calcd: C, 64.24; H, 9.95; N, 8.64. Found: C, 63.88; H, 9.60; N, 8.33.

Example 22: Preparation of N-(6-aminohexan-1-yl)-2-dodecyloxy-5-phenylbenzamide hydrochloride

a) N-[6-(tert-Butoxycarbonyl)aminohexan-1-yl]-2-dodecyloxy-5-phenylbenzamide

A mixture of palladium acetate (4.5 mg, 5 mmol %) and 1,4-bis(diphenylphosphino)butane (8.5 mg, 5 mmol %) in anhydrous DME (3.5 mL) under argon was heated at 70°C for 40 seconds and gradually cooled to room temperature. The compound of Example 18(c) (250 mg, 0.4 mmol) was added, followed by phenylboric acid (54 mg, 0.44 mmol), sodium carbonate (93 mg, 0.88 mmol) and water (0.15 mL). The reaction was heated at 70°C for 2 h and 100°C for 10 h. The reaction mixture was diluted with ethyl acetate and washed with water, 10% HCl, and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting crude mixture was purified by flash column chromatography (silica, 15% and 20% ethyl acetate / hexane) to afford the title compound (97 mg, 42%) as a white solid. MS (ES) m/e 581.4 $[M+H]^+$, 525.4, 481.4.

b) N-(6-Aminohexan-1-yl)-2-dodecyloxy-5-phenylbenzamide hydrochloride

Following the procedure of Example 19(b), except substituting the compound of Example 22(a) (66 mg, 0.11 mmol) for N-[6-(tert-butoxycarbonyl)aminohexan-1-yl)-2-dodecyloxy-5-(2-phenylethynyl)benzamide, the title compound (59 mg, 96%) was prepared as an amorphous white solid. Anal. ($C_{31}H_{49}O_2N_2Cl \cdot H_2O$) calcd: C, 69.57; H, 9.61; N, 5.23. Found: C, 69.72; H, 9.35; N, 5.17.

Example 23: Preparation of N-(2-piperazinyl)phenyl-2-dodecyloxybenzamide hydrochloride

a) 1,1-Dimethylethyl 4-(2-nitrophenyl)-1-piperazinecarboxylate

To a stirred solution of tert-butyl 1-piperazine-carboxylate (1.45 g, 7.8 mmol) in anhydrous dimethyl sulfoxide (21 mL) was added 1-fluoro-2-nitrobenzene (1 g, 7.1 mmol) and sodium bicarbonate (1.2 g, 14.2 mmol). The reaction was stirred at 95°C for 20 h. The reaction was diluted with ice-cold 10% HCl and extracted with ethyl acetate (2x). The combined organic layers were extracted exhaustively with cold saturated $NaHCO_3$ solution; the resulting basic extracts were combined, acidified to pH 2 with 10% HCl, and washed with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (2.3 g, >99%) as a viscous yellow oil: MS (ES) m/e 308 $[M+H]^+$, 252, 208.

b) 1,1-Dimethylethyl 4-(2-aminophenyl)-1-piperazinecarboxylate

Following the procedure of Example 11(c), except substituting the compound of 23 (a) (254 mg, 0.83 mmol) for 6-(tert-butoxycarbonyl)amino-N-[[(2-dodecyloxy-5-nitro)phenyl]methyl]-N-methylhexanamide, the title compound (199 mg, 87%) was prepared as a white solid. MS (ES) m/e 278.2 $[M+H]^+$, 222, 178.2.

c) N-(2-Piperazinyl)phenyl-2-dodecyloxybenzamide hydrochloride

Following the procedure described in Example 15, except substituting the compound of Example 23(b) (199 mg, 0.72 mmol) for N-BOC-1,6-diaminohexane

hydrochloride and 4N HCl/dioxane for trifluoroacetic acid, the title compound (138 mg, 94%) was prepared as a hygroscopic colorless solid. Anal. ($C_{29}H_{44}O_2N_3Cl \cdot 0.75\ H_2O$) calcd: C, 67.55; H, 8.89; N, 8.15. Found: C, 67.53; H, 8.58; N, 7.82.

Example 24: Preparation of N-(3-piperazinyl-4-methoxy)phenyl-2-dodecyloxybenzamide hydrochloride

a) 1,1-Dimethylethyl 4-(5-amino-2-methoxyphenyl)-1-piperazinecarboxylate

The title compound can be made according to the experimental disclosure found in European Patent Application 0 533 267 A1, published March 24, 1993, specifically on page 16, Intermediate 21, which is incorporated herein by reference.

b) N-(3-Piperazinyl-4-methoxy)phenyl-2-dodecyloxybenzamide hydrochloride

Following the procedure described in Example 15, except substituting the compound of Example 24(a) (127 mg, 0.41 mmol) for N-BOC-1,6-diaminohexane hydrochloride and 4N HCl/dioxane for trifluoroacetic acid, the title compound (182 mg, 93%) was prepared as a white powder. Anal. ($C_{30}H_{46}O_3N_3Cl \cdot 1.75\ H_2O$) calcd: C, 63.92; H, 8.85; N, 7.45. Found: C, 63.75; H, 8.71; N, 7.50.

Example 25: Preparation of N-(3-Piperazinyl-4-methoxy)phenyl-2-benzylbenzamide dihydrochloride

Following the procedure described in Example 15, except substituting the compound of Example 24(a) (176 mg, 0.57 mmol) for N-BOC-1,6-diaminohexane hydrochloride, benzyl bromide for 1-iodododecane, and 4N HCl/dioxane for trifluoroacetic acid, the title compound (217 mg, 87%) was prepared as an amorphous white solid. Anal. ($C_{25}H_{29}O_3N_3Cl_2 \cdot 2.25\ H_2O$) calcd: C, 56.55; H, 6.16; N, 7.91. Found: C, 56.90; H, 6.42; N, 7.81.

Example 26: Preparation of 5-(3-aminopropyl)-2-dodecyloxy-N-(3-piperazinyl-4-methoxy)phenyl- benzamide trihydrochloride

Following the procedure described in Example 18, except substituting the compound of Example 24(a) (127 mg, 0.41 mmol) for N-BOC-1,6-diaminohexane hydrochloride, the title compound (49.5 mg, 94%) was prepared as an amorphous light pink solid. Anal. ($C_{33}H_{55}O_3N_4Cl_3 \cdot 1.5\ H_2O$) calcd: C, 57.50; H, 8.48; N, 8.13. Found: C, 57.28; H, 8.36; N, 8.11.

PROTEIN KINASE C INHIBITION ASSAY

PKC is purified (>90 percent) from rat brain according to Walton *et al.* (Walton, G.H., Bertics, P.J., Hudson, L.G., Vedvick, T.S. & Gill, G.N. *Anal Biochem 161*: 425-

437 [1987]) and Woodget & Hunter (Woodget, J.R. & Hunter, T. *J Biol Chem 268*: 4836-4843 [1987]). The enzyme is stored frozen in 16% glycerol and 0.01% Triton X-100.

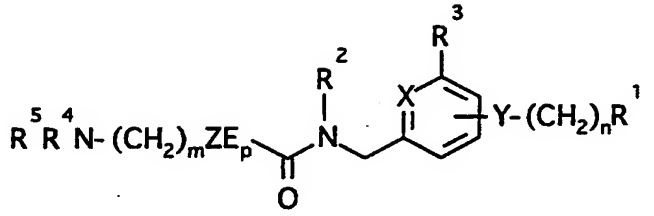
PKC activity is assayed as Ca^{2+} / phospholipid-dependent transfer of ^{32}P-labeled phosphate from ATP to a synthesized peptide substrate (purchased from Bachem). Reaction mixtures (50 mL) contain, in addition to purified PKC: 10 mM Tris, pH 7.5; 1.1 mM $CaCl_2$; 10 mM $MgCl_2$; 1.0 mM EGTA; 40 mg/mL phosphatidyl serine; 1 mg/mL Diolein; 100 mg/mL Bachem peptide; 0.5 microcuries of g-^{32}P-ATP (specific activity. = 6000 Curies / mmole; 10 mM final concentration); and various concentrations of test compounds or extracts. The reaction is initiated by addition of ATP, and is terminated after 20 minutes at 37 °C by spotting the mixture onto Whatman P81 paper squares, which are then washed in 0.5% phosphoric acid, dried with acetone, and assayed for ^{32}P-radioactivity by liquid scintillation spectrometry. The IC_{50}, i.e., the concentration giving 50% inhibition of PKC activity, is determined by the equation [Log $IC_{50} = X_S+d(Sx - 0.5)$] where Sx is the sum of the percentages of enzyme inhibition at each concentration, d is the log of the concentration drop per interval, and X_S is the log of the highest concentration tested.

The compounds of this invention show activity as PKC inhibitors and have IC_{50} values in the range of 0.001 to 150 micromolar. Given the disclosure herein, one of ordinary skill in the art can utilize the present assay in order to determine which compounds of formula (I) or (II) are inhibitors of PKC.

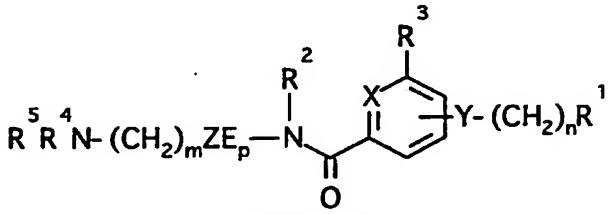
The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration it is believed that one skilled in the art can, use the preceding description, utilize the present invention to its fullest extent. Therefore any examples are to be construed as merely illustrative and not a limitation on the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof:



Formula (I)



Formula (II)

wherein

R^1 is hydrogen, lower alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

R^2 is hydrogen or lower alkyl;

R^3 is hydrogen, $C{\equiv}CR^6$ or $-(CH_2)_kR^6$;

R^4 and R^5, independently from one another, are hydrogen or lower alkyl; or R^4 and R^5, together with the nitrogen to which they are bound, form a saturated or unsaturated 5-, 6-, or 7-membered ring;

R^6 is aryl, $-CO_2R^7$, $-NHC(O)R^7$, $-NR^7R^8$, or $-C(O)NR^7R^8$;

R^7 and R^8, independently from one another, are hydrogen, or alkyl, provided that when R^6 is $-CO_2R^7$, R^7 is not hydrogen;

E is CH-R^9, wherein R^9 is hydrogen, alkoxy, -OH or $-NR^{10}R^{11}$;

R^{10} and R^{11}, independently from one another, are hydrogen or lower alkyl, or wherein R^{10} and R^{11}, together with the nitrogen to which they are bound, form a saturated or unsaturated 5-, 6-, or 7-membered ring;

X is CH or N;

Y is $-CH_2$, -O, -S, -N or $C(O)NR^{12}R^{13}$, wherein R^{12} and R^{13}, independently from one another are hydrogen or alkyl, and further wherein Y is positioned on the central aromatic ring either ortho, meta or para relative to the amide containing side chain;

Z is $-CH_2$, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

k is an integer between 0 and 10;

m is an integer between 0 and 10, provided that m is 0 only when Z is optionally substituted aryl or optionally substituted heteroaryl, and further, provided that when m is 0 and Z is optionally substituted aryl or optionally substituted heteroaryl, R^4 and R^5 are not hydrogen or lower alkyl;

n is an integer between 6 and 20; and

p is an integer between 0 and 1.

2. The compound as claimed in claim 1, wherein R^1 is hydrogen, lower alkyl or optionally substituted aryl.

3. The compound as claimed in any of claims 1 or 2, wherein R^2 is hydrogen, methyl or ethyl.

4. The compound as claimed in any of claims 1 to 3, wherein R^3 is hydrogen or $-(CH_2)_kR^6$.

5. The compound as claimed in any of claims 1 to 4, wherein R^4 and R^5 are hydrogen or, together with the nitrogen to which they are bound, form a saturated six-membered ring.

6. The compound as claimed in any of claims 1 to 5, wherein R^6 is $-NR^7R^8$ or $-CO_2R^7$.

7. The compound as claimed in any of claims 1 to 6, wherein R^7 and R^8, independently , from one another, are hydrogen or methyl, provided that when R^6 is $-CO_2R^7$, R^7 is not hydrogen.

8. The compound as claimed in any of claims 1 to 7, wherein E is $CH-R^9$, wherein R^9 is hydrogen or $NR^{10}R^{11}$, wherein R^{10} and R^{11} are each hydrogen.

9. The compound as claimed in any of claims 1 to 8, wherein X is CH or N.

10. The compound as claimed in any of claims 1 to 9, wherein Y is oxygen and is ortho relative to the amide containing side chain.

11. The compound as claimed in any of claims 1 to 10, wherein Z is $-CH_2$.

12. The compound as claimed in claim 1 which is:

(*R*)-2,6-diamino-N-[[2-dodecyloxy)phenyl]methyl]-N-methylhexanamide;

6-amino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylhexanamide;

6-amino-N-methyl-N-[[[2-(8-phenyl)octyloxy]phenyl]methyl]hexanamide;

(*R*)-2,6-diamino-N-methyl-N-[[[2-(8-phenyl)octyloxy]phenyl]methyl] hexanamide;
6-amino-N-[[2-(hexadecyloxy)phenyl]methyl]-N-methylhexanamide;
4-amino-N-[[2-(dodecyloxy)phenyl]methyl]-N-methylbutanamide;
6-amino-N-[[3-(dodecyloxy)phenyl]methyl]-N-methylhexanamide;
N-[[2-(dodecyloxy)phenyl]methyl]-N-methyl-6-morpholinohexanamide;
N-[[2-(dodecyloxy)phenyl]methyl]-N-[methylhexanamido]-6-N′, N′, N′-trimethylammonium bromide;
6-amino-N-methyl-N-[[[2-(8-phenyl)octyl]phenyl]methyl]hexanamide;
N-[[(5-amino-2-dodecyloxy)phenyl]methyl]-6-amino-N-methylhexanamide;
6-amino-N-[[2-dodecyloxy-5-[(1-oxooctyl)amino]phenyl]methyl]-N-methylhexanamide;
6-amino-N-[[2-(dodecyloxy)phenyl]methyl]hexanamide;
6-amino-N-[(3-dodecyloxy)-2-pyridinyl]methyl]-N-methylhexanamide;
N-(6-aminohexane-1-yl)-2-dodecyloxybenzamide;
N-(6-aminohexane-1-yl)-2-dodecyloxy-5-(2-methoxycarbonylethyl)benzamide;
N-[4-(2-amino)ethyl]phenyl-2-dodecyloxybenzamide;
N-(6-aminohexane-1-yl)-5-[(3-amino)propyl]-2-dodecyloxybenzamide;
N-[3-(3-amino)propyl]phenyl-2-dodecyloxybenzamide;
N-[2-(3-amino)propyl]phenyl-2-dodecyloxybenzamide;
5-(2-phenylethynyl)-N-(6-aminohexan-1-yl)-2-dodecyloxybenzamide;
5-(2-phenylethyl)-N-(6-aminohexan-1-yl)-2-dodecyloxybenzamide;
6-amino-N-[[3-[(N-dodecyl)aminocarbonyl]phenyl]methyl]hexanamide;
N-(6-aminohexan-1-yl)-2-dodecyloxy-5-phenylbenzamide;
N-(2-piperazinyl)phenyl-2-dodecyloxybenzamide;
N-(3-piperazinyl-4-methoxy)phenyl-2-dodecyloxybenzamide; or
5-(3-aminopropyl)-2-dodecyloxy-N-(3-piperazinyl-4-methoxy)phenylbenzamide.

13. A pharmaceutical composition comprising a compound of formula (I) or formula (II) as claimed in any of claims 1 to 11 and a pharmaceutically acceptable carrier or diluent therefor.

14. A method of treatment of a PKC-mediated disease state in a mammal, which comprises administering to said mammal in need thereof, an effective amount of a compound of formula (I) or formula (II), or a pharmaceutically acceptable salt thereof as claimed in any of claims 1 to 12.

15. The method as claimed in claim 14 wherein the PKC-mediated disease state is chronic inflammation, psoriasis, a neurological disorder or cancer.

16. A method of treating a chronic inflammatory condition in a human in need thereof, which method comprises administering to said human an effective amount of a compound of formula (I) or formula (II), or a pharmaceutically acceptable salt thereof as claimed in any of claims 1 to 12.

17. A method of inhibiting PKC in a mammal in need thereof, which method comprises administering to said mammal an effective amount of a compound of formula (I) or formula (II), or a pharmaceutically acceptable salt thereof as claimed in any of claims 1 to 12.

INTERNATIONAL SEARCH REPORT

Inte...ational application No.
PCT/US94/14684

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/238.2, 255, 351, 542, 616, 617, 618, 620, 622, 626; 544/168, 393; 546/300; 560/42; 564/157, 162, 165, 171, 177, 183, 196.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5,238,962 (DA PRADA ET AL) 24 August 1993, column1, lines 11-37.	1-13
X	US, A, 3,631,102 (VENKATACHALA ET AL.) 28 December 1971, column 1, lines 26-56.	1-13
X	US, A, 2,665,309 (BRUCE ET AL.) 05 January 1954, column 1, lines 1-30.	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 26 MARCH 1995	Date of mailing of the international search report 06 APR 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RICHARD L. RAYMOND Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

Inte..ational application No.
PCT/US94/14684

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/165, 31/24, 31/44, 31/495, 31/535; C07C 229/38, 235/50, 237/08; C07D 213/64, 241/04, 265/30.

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/238.2, 255, 351, 542, 616, 617, 618, 620, 622, 626; 544/168, 393; 546/300; 560/42; 564/157, 162, 165, 171, 177, 183, 196.